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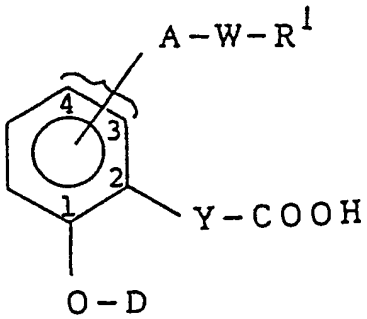
(54) Phenylalkan(en)oic acids.

(57) The phenylalkan(en)oic acids of the formula:



(I)

wherein the substituants are defined as in the disclosure, possess an antagonism on leukotriene B_4, and therefore, are useful for the prevention and treatment of several diseases induced by leukotriene B_4.

EP 0 405 116 A2

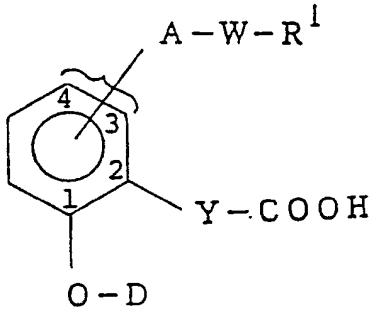
PHENYLALKAN(EN)OIC ACIDS

Summary

This invention is related to phenylalkan(en)oic acids which are useful for medicines.

More particularly, this invention is related to:

1) phenylalkan(en)oic acids of the formula:



(I)

(wherein all of the symbols are the same meanings as hereinafter defined) and non-toxic salts thereof,

2) processes for the preparation of them and

3) antagonistic agents on leukotriene (abbreviated as LT hereinafter) B_4 containing them as active ingredient.

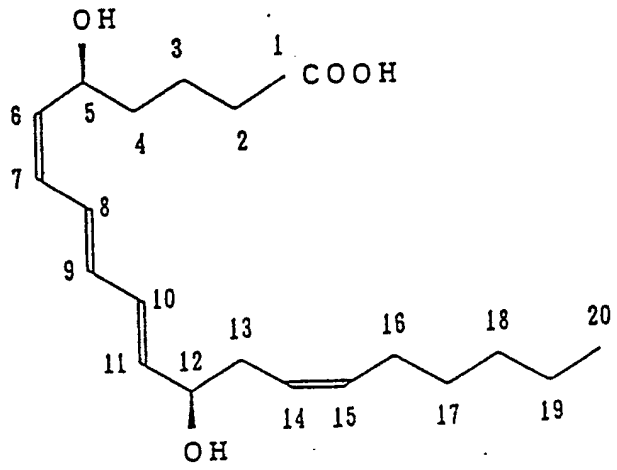
Background

The metabolic routes, in which various compounds are biosynthesized from the same mother compound, i.e. arachidonic acid, are called "Arachidonate cascade" as a whole.

Arachidonic acid is metabolized by the action of lipoxygenase, e.g. 5-lipoxygenase, 12-lipoxygenase, and 15-lipoxygenase, to 5-hydroperoxyeicosatetraenoic acid (abbreviated as HPETE hereinafter), 12-HPETE and 15-HPETE, respectively.

These HPETEs are converted into 5-hydroxyeicosatetraenoic acid (abbreviated as HETE hereinafter), 12-HETE and 15-HETE, respectively, by the action of peroxidase which convert a hydroperoxy group to a hydroxy group. Furthermore, LTA_4 is also produced from 5-HPETE. LTA_4 is converted into LTB_4 and LTC_4. LTC_4 is converted into LTD_4 by the action of γ-glutamyl transpeptidase. Moreover, it has been defined that LTD_4 is metabolized to LTE_4 (see Biochem. Biophys. Res. Commun., 91 , 1266 (1979) and Prostaglandins, 19 (5) , 645 (1980)).

Moreover, the action of LTB_4 has been gradually identified recently. Namely, it as been identified that LTB_4 having the following structure:



(wherein the double bonds between 6th- and 7th- carbon, 8th- and 9th-carbon, 10th- and 11th- carbon and 14th- and 15th-carbon, are Z, E, E and Z, respectively), possesses a powerful action of polymorphonuclear leukocytes (PMNLs) accumulation and PMNLs adhesion, and PMNLs degranulation (see Nature, 286, 264 (1980), Proc. Nat. Acad. Sci. USA, 78 , 3887 (1981) and J.Biol. Chem., 256, 5317 (1981)). Moreover it has been considered that LTB_4 promotes the release of arachidonic metabilites by attacking various cells as it has the powerful action like calcium ionophore (see J. Biol. Chem., 257 , 4746 (1982)).

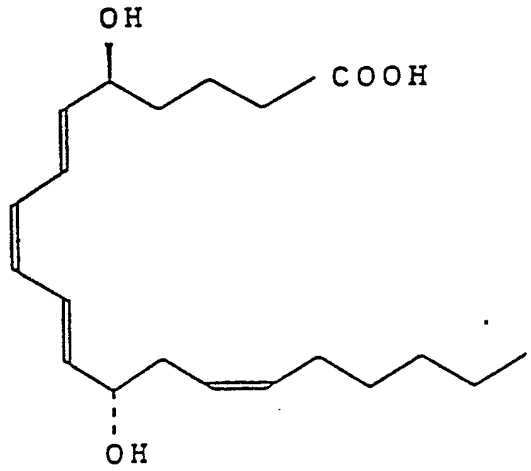
Moreover, LTB_4 in high concentration has been detected at the sites of various inflammation, for example, rheumatism, spinal arthritis (see Klickstein L.B., Shapleigh, C. and Goetzl, E.J. (1980) J.Clin. Invest., 66 , 1166-1170), gout (Rae, S.A., Davidson, E.M. and Smith, M.J.H. (1982) Lancet II 1122-1123), psoriasis (see Grabbe, J., Czarnetzki, B.M., Rosenbach, T. and Mardin, M. (1984) J. Invest. Dermatol., 82 , 477-479), ulceractive colitis (see Sharon, P. and Stension, W.F. (1984) Gastroenterology 86 , 453-460), respiratory disease (see O'Driscoll, B.R., Cromwell, O. and Kay, A.B. (1984) Clin. Exp., Immunol., 55 397-404). The fact described above shows that LTB_4 is deeply related to various inflammation.

Accordingly, the antagonistic agents on LTB_4 are considered to be useful as anti-inflammatory agents and antiallergic agents.

Related arts

In recent research, some compounds having an antagonism on LTB_4 have been reported.
For example,

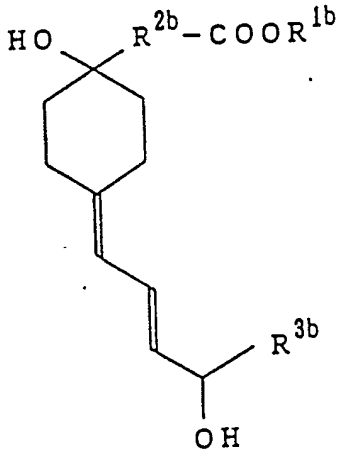
1) in the literatures (Feinmark, J., Lindgren, J.A., Claesson, H.E., Malmsten, C., and Samuelsson, B. (1981) FEBS Lett., 136 , 141-144; Showell, H. J., Oherness, I.G., Marfat, A., and Corey, E.J. (1982) Biochem, Biophy. Res. Commun., 106 , 741-747), the compound of the formula:



(a)

has been disclosed,

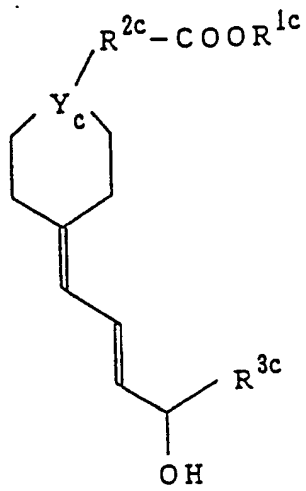
2) in the specification of Japanese Patent Kakai No. 59-33258, i.,e. Derwent accession No. 84-173740/28, the compounds of the formula:



(b)

wherein R^{1b} is hydrogen or C1-4 alkyl;
R^{2b} is C1-8 alkylene; and R^{3b} is hydrogen, C1-15 alkyl or the group of the formula $-CH_2-A_b-R^{4b}$ (wherein A_b is cis-vinylene or ethynylene; and
R^{4b} is C1-12 alkyl); have been disclosed,

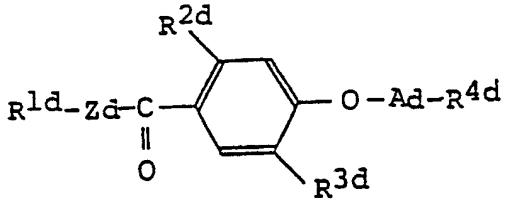
3) in the specification of Japanese Patent Kokai No. 59-95249, i.e. Derwent accession No. 84-84453/14, the compounds of the formula:



(c)

wherein Yc is nitrogen or aminomethyl; R^{1c} is hydrogen or C1-4 alkyl; R^{2c} is C1-8 alkylene; and R^{3c} is C1-15 alkyl or the group of the formula: $-CH_2-Ac-R^{4c}$
(wherein Ac is cis-vinylene or ethynylene; and R^{4c} is C1-12 alkyl); have been disclosed and more recently

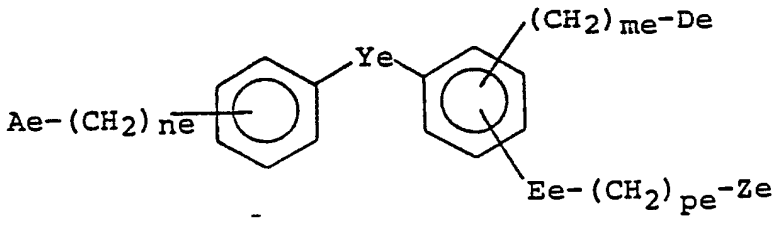
4) in the specification of Japanese Patent Kokai No. 63-188644, i.e. European Patent Publication No. 276065, the comnpounds of the formula:



(d)

(wherein R^{1d} hydrogen or $-COOR^{d'}$, Zd is-(CH_2)nd- or phenylene (nd is 1-8); R^{2d} is hydroxy, halogen or $-O-(CH_2)$md-Yd; R^{3d} is C1-6 alkyl, C1-6 alkanoyl, C2-4 alkenyl, C1-4 alkoxy, C1-3 alkyl substituted by hydroxy or $-CH_2$-Dd; Ad is bond or straight-chain or branched-chain C1-10 alkylidene; R^{4d} is C1-6 alkyl, C2-6 alkenyl or C2-6 alkynyl, hydroxy, -CN, halogen, $-N_3$, $-NR^{5d}R^{6d}$, $-COR^{7d}$, -S(O)pd-(C1-4 alkyl), 1,2,4-triazol-1-yl, 5-tetrazolyl which may be substituted by C1-4 alkyl or $-(CH_2)$gdCOOR$^{d'}$, phenyl which may be substituted by1 or 2 of halogen, -CN, C1-3 alkyl, $-CF_3$, $-CH_2CN$, $-CH_2Br$, C1-4 alkoxy, -S(O)pd-(C1-4 alkyl), acetenyl, acetyl, $COOR^{d'}$, 5-tetrazolyl, or 5-tetrazolyl substituted by C1-4 alkyl or -(CH2)gd-$COOR^{d'}$ (each $R^{d'}$ is hydrogen or C1-4 alkyl; md is 1-4; gd is 1-4; Yd is hydrogen or -CN; Dd is halogen, C1-4 alkoxy or -S-(C1-4 alkyl)); R^{5d} and R^{6d} are independently hydrogen, C1-3 alkyl or C2-4 alkanoyl, or R^{5d} and R^{6d}, taken together with a nitrogen atom to which they are attached, form morpholino; R^{7d} is hydroxy, C1-4 alkoxy, halogen, $-NR^{5d}R^{6d}$, -NHOH, 5-tetrazolylamino or C1-3 alky; each pd is 0-2; with the proviso that when Ad is bond, R^{4d} should be C1-6 alkyl or optionally substituted phenyl, and when one of R^{5d} and R^{6d} is C2-4 alkanoyl, then the other should be hydrogen; and the pharmaceutically acceptable salts have been disclosed,

5) in the specification of Japanese Patent Kokai No. 63-188646, i.e. European Patent Publication No. 276064, the compounds of the formula;

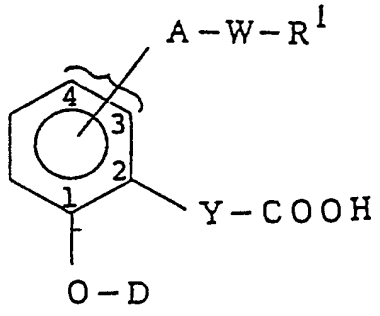


(e)

(wherein Ae and De are independently -CN, -COOR^{1e} or 5-tetrazolyl;
ne is 0 or 1;
Ye is -O-, -CO-, -CH_2CO-, -C(=NOH)-, -CHOH-, -CH_2- or -C(=CH_2);
me is 0-3;
Ee is -O- or -CH_2-;
pe is 0-16;
Ze is hydrogen or -Ge-Qe;
Ge is bond, -O-, -S(O)te-, -NH- or -CH=CH-,
Qe is phenyl or phenyl substituted by 1 or 2 of halogen, C1-3 alkyl, C1-3 alkoxy, nitro, amino, trifluoromethyl, hydroxy and -S(O)pe -(C1-3 alkyl); pe and te are each 0-2; R^{1e} is hydrogen or C1-3 alkyl); and the pharmaceutically acceptable salts have been disclosed.

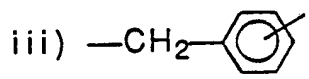
Disclosure of the invention

The present invention is related to
1) phenylalkan(en)oic acid of the formula:



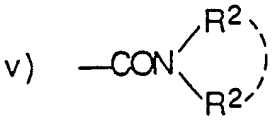
(I)

wherein A is
i) -NHCO-,
ii) -O-
iii) -$NHSO_2$-,
iv) -CO-
v) -CH_2- or
vi) -CH(OH)-;
W is i) C1-13 alkylene,
ii) phenylene or

iii)  ;

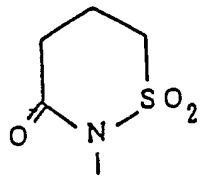
R^1 is i) hydrogen,
ii) C1-4 alkyl,
iii) -COOH,
iv) saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero

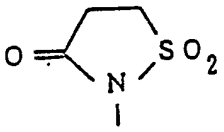
atom or saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom substituted by an oxo group,

v) 

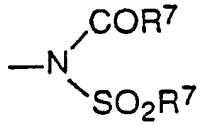
vi) $-CO_2OH$;

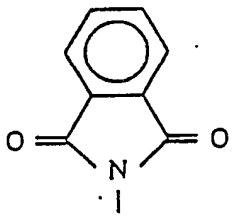
A, taken together with W and R^1, is

i)  ,

ii)  ,

iii) $-N-(SO_2R^6)_2$,

iv)  or

v)  ;

two R^2 are, same or different,

i) hydrogen,

ii) C1-4 alkyl or

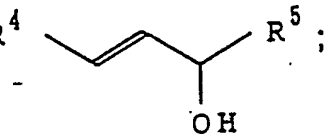
iii) 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur in total, or two R^2, taken together with a nitrogen to which they are attached, form saturated or unsaturated,

i) 7-14 membered, bi-or tri-cyclic hetero ring containing one nitrogen as a hetero atom, or

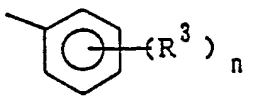
ii) 4-7 membered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total ;

Y is ethylene or vinylene;

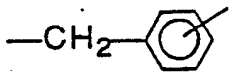
D is i) -Z-B or

ii) 

Z is C3-11 alkylene or alkenylene

B is  ; or

Z, taken together with B, is C3-22 alkyl;
R^3 is i) hydrogen,
ii) halogen,
III) C1-8 alkyl, alkoxy or alkylthio, or
iv) C2-8 alkenyl, alkenyloxy or alkenylthio;
n is 1-3;
R^4 is C1-7 alkylene;
R^5 is i) C1-12 alkyl,
ii) C2-12 alkenyl,
iii) C5-7 cycloalkyl or
iv) phenethyl or phenethyl wherein the ring is substituted by one C1-4 alkoxy;
Two R^6 are, same or different,
i) C1-7 alkyl,
ii) benzyl or
iii) phenyl or phenyl wherein the ring is substituted by one C1-4 alkyl; and
Two R^7 are, same or different, C1-4 alky;
with the proviso that
i) -A-W-R^1 should bind to 3- or 4- carbon in benzene ring, and
ii) when W is phenylene or



A should not represent -O-, -CO-, -CH_2- or -CH(OH)-;
and non-toxic salts thereof,
2) processes for the preparation of them and
3) antagonistic agent on leukotriene B_4 containing them as active ingredient.

The present invention includes all isomers unless otherwise specified. For example, alkyl, alkoxy, alkenyl, alkenyloxy, alkylthio, alkenylthio, alkylene and alkenylene groups mean straight-chain or branched-chain alkyl, alkoxy, alkenyl, alkenyloxy, alkylthio, alkenylthio, alkylene and alkenylene groups, respectively, and the double-bond in alkenylene, alkenyl, alkenyloxy and alkenylthio groups include E, Z and the mixture of E and Z. In case of existing branched-chain alkyl group etc., the present invention includes the isomers caused by existing asymmetrical carbon atoms.

In the formula (I), C1-13 alkylene group shown by W are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene, dodecamethylene, tridecamethylene group and isomers thereof.

In the formula (I), C1-4 alkyl group shown by R^1, R^2, substituent in R^6, and R^7 are methyl, ethyl, propyl, butyl group and isomers thereof.

In the formula (I), 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing one nitrogen as a hetero atom, shown by R^1 are, for example, pyrrole, pyridine ring and partially or fully saturated rings thereof, such as pyrrolidine. These rings may be substituted by one oxo group. 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur

in total, shown by R^2 are, for example, thiazole, isothiazole, thiadiazoline ring and partially or fully saturated rings thereof.

In the formula (I), saturated or unsaturated, 7-14 membered, bi- or tri-cyclic hetero ring containing one nitrogen as a hetero atom, shown by two R^2, taken together with a nitrogen to which they are attached are, for example, indole, isoindole, quinoline, isoquinoline, carbazole, acridine ring and partially or fully saturated rings thereof. Saturated or unsaturated, 4-7 membered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total, shown by two R^2, taken together with a nitrogen are, for example, oxazole, isooxazole, furazan ring and partially or fully saturated rings thereof and morpholine ring.

In the formula (I), C3-11 alkylene and alkenylene groups shown by Z are trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene group and isomers thereof and the groups containing 1 to 3 of double bonds therein.

In the formula (I), C1-8 alkyl group shown by R^3 are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl group and isomers thereof. C1-8 alkoxy group shown by R^3 are methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy group and isomers thereof. C1-8 alkylthio group shown by R^3 are methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio, heptylthio, octylthio group and isomers thereof.

In the formula (I), C2-8 alkenyl group shown by R^3 are the groups containing 1 to 3 of double bonds in ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl group and isomers thereof. C2-C8 alkenyloxy group shown by R^3 are the groups containing 1 to 3 of double bonds in ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy group and isomers thereof. C2-C8 alkenylthio group shown by R^3 are the groups 1 to 3 of double bonds in ethylthio, propylthio, butylthio, pentylthio, hexylthio, heptylthio, octylthio group and isomers thereof. Halogen shown by R^3 are, fluorine, chlorine, bromine and iodine atom.

In the formula (I), C3-22 alkyl group shown by Z, taken together with B are propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl group and isomers thereof.

In the formula (I), C1-7 alkylene group shown by R^4 are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene group and isomers thereof.

In the formula (I), C1-12 alkyl group shown by R^5 are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl group and isomers thereof. C2-12 alkenyl group shown by R^5 are the groups containing 1 to 3 of double bonds in ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl group and isomers thereof. C5-7 cycloalkyl group shown by R^5 are cyclopentane, cyclohexane, cycloheptane. C1-4 alkoxy group shown by substituents in R^5 are methoxy, ethoxy, propoxy, butoxy group and isomers thereof.

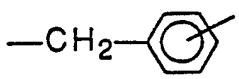
In the formula (I), C1-7 alkyl group shown by R^6 are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl group and isomers thereof.

Comparison with related arts

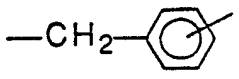
The compounds of the formula (I), of the present invention are quite novel.

More concretely, the compounds wherein W represents an alkylene, of the present invention are quite novel in structure. Furthermore, it can not be expected from the information of the related arts that the compounds having these structures, possess an antagonism on leukotriene B_4.

The compounds wherein W represents a phenylene or the group of the formula:



of the present invention are also quite novel. The compounds of the formula (d) have the structure in which the group corresponding to A in the formula (I) is carbonyl group, and those of the formula (e) have the structure in which the group corresponding to A in the formula (I) is oxy, carbonyl, methylene or hydroxymethylene group. On the other hand, the compounds wherein W represents a phenylene or the group of the formula:



of the present invention, have the group of the formula: -NHCO- or -$NHSO_2$- as the group A. Therefore, the compounds of the present invention are quite different from the related arts in structure in that the groups shown by A represent quite different groups.

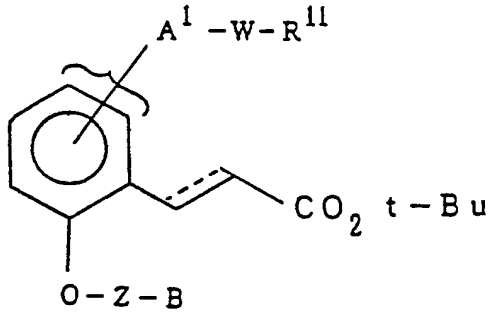
Furthermore, it can not be expected that an antagonism on leukotriene B_4 was held in the compounds wherein oxy, carbonyl, methylene or hydroxymethylene group is replaced by the groups of the formula -NHCO- or -$NHSO_2$-.

Salts

The compounds of the formula (I) may be converted into the corresponding salts by the known method. Non-toxic and water-soluble salts are preferable. Suitable salts, for example, are followings:
salts of alkaline metal (sodium, potassium etc.),
salts of alkaline earth metal (calcium, magnesium etc.),
ammonium salts, salts of pharmaceutically acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine etc.).

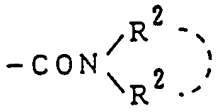
Process for the preparation of the compounds of the present invention

The compounds of the formula (I), of the present invention may be prepared by
1) saponificating the compound of the formula:



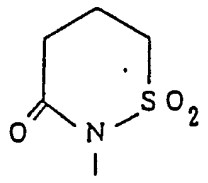
(II)

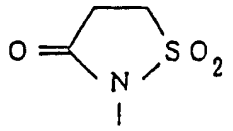
wherein A^1 is
i) -NHCO- or
ii) -$NHSO_2$-;
R^{11} is
i) the group of R^{1a}
(wherein R^{1a} is hydrogen, saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom, unsubstituted or
substituted by an oxo group or
C1-C4 alkyl),
ii) -CO_2H or
iii) the group shown by:

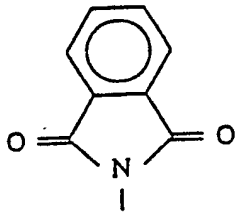


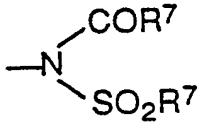
;

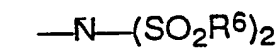
or
A^1, taken together with W and R^{11}, is

i) 

ii) 

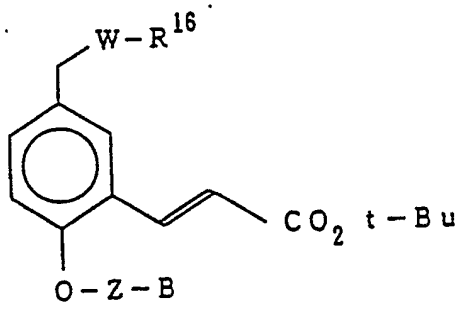
iii) 

iv) 

v) 

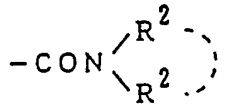
 is ethylene or vinylene;

t-Bu is tert-Butyl group; and
the other symbols are the same meanings as described hereinbefore;
or the compounds of the formula:



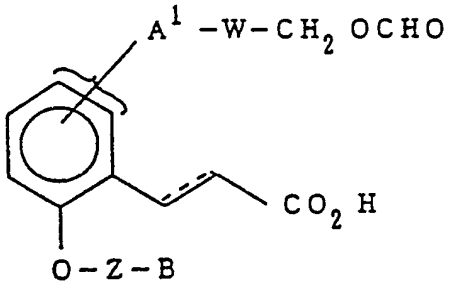
(XI)

wherein R^{16} is
i) $-CO_2H$ or
ii) the group of the formula:



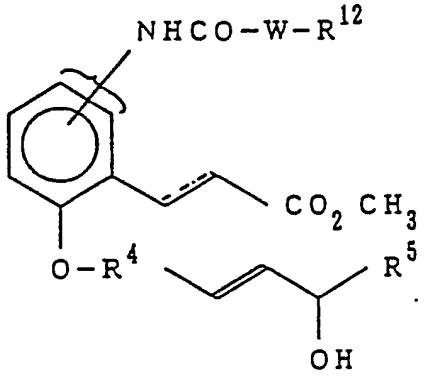
; and

the other symbols are the same meanings as described hereinbefore;
with using an acid (formic acid, trifluoroacetic acid etc.) in an inert organic solvent (methanol, tetrahydrofuran etc.),
2) saponificating the compound of the formula:



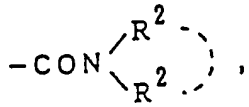
(III)

wherein, all of the symbols are same meaning as described hereinbefore;
the compound of the formula:



(IV)

wherein R^{12} is
i) the group of R^{1a}, ii) the group shown by

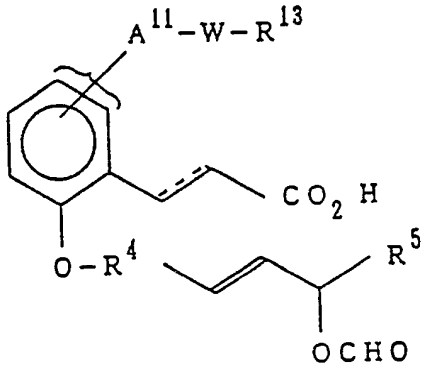


,

iii) $-CO_2CH_3$ or

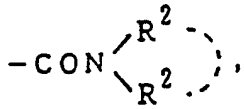
IV)  ; and

the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



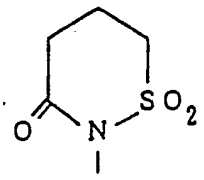
(V)

wherein A^{11} is $-NHSO_2-$;
R^{13} is
i) the group of $-R^{1a}$,
ii) the group shown by

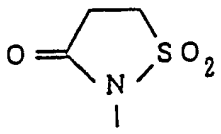


iii) $-CH_2OCHO$ or
iv) $-CO_2H$;
A^{11}, taken together with W and R^{13}, is

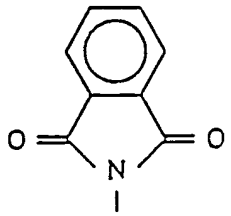
i)



ii)



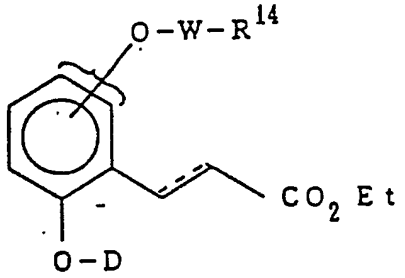
iii)



iv) $-N\begin{matrix}COR^7\\SO_2R^7\end{matrix}$ or

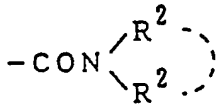
v) $-N(SO_2R^6)_2$; and

the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



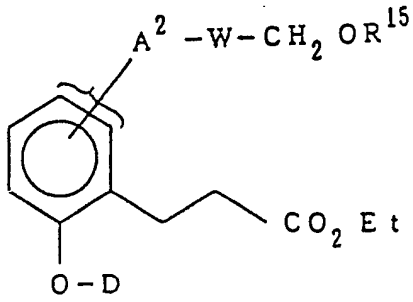
(VI)

wherein Et is ethyl;
R^{14} is
i) the group of $-R^{1a}$,
ii) the group shown by



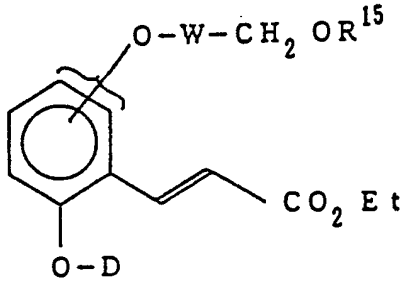
or

iii) $-CO_2Et$; and
the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



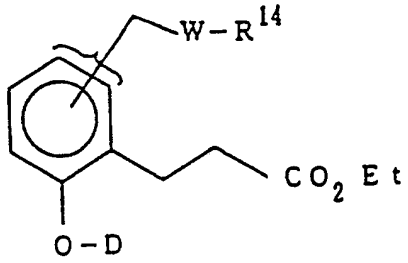
(VII)

wherein A^2 is
i) -O- or
ii) $-CH_2-$;
R^{15} is
i) hydrogen or
ii) acetyl group; and
the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



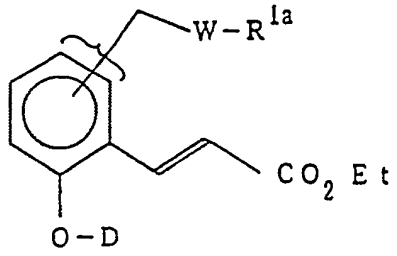
(VIII)

wherein all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:



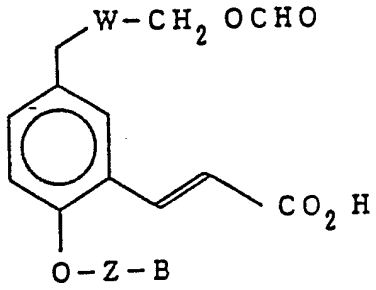
(IX)

wherein all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:



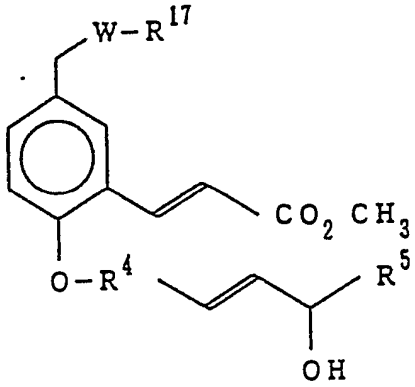
(X)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula;



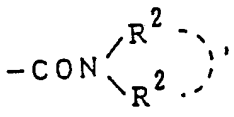
(XII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:

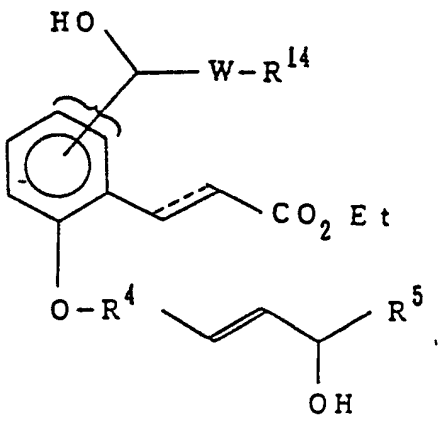


(XIII)

wherein R^{17} is
i) the group shown by

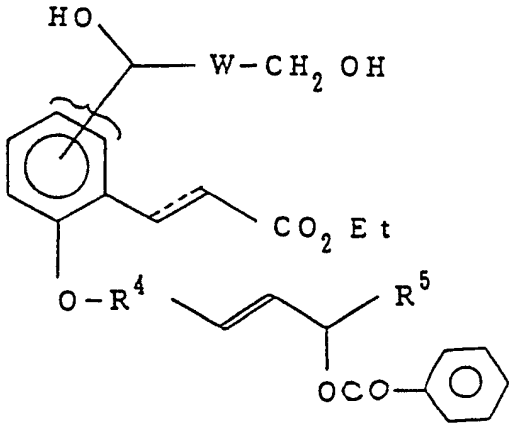


ii) $-CH_2OH$ or
iii) $-CO_2H$; and
the other symbols are the same meanings as described hereinbefore;, the compound of the formula:



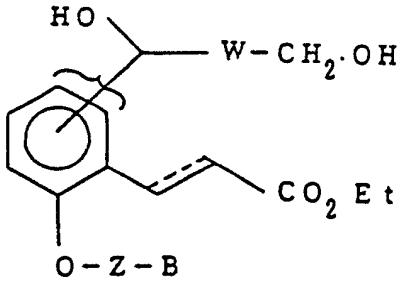
(XV)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



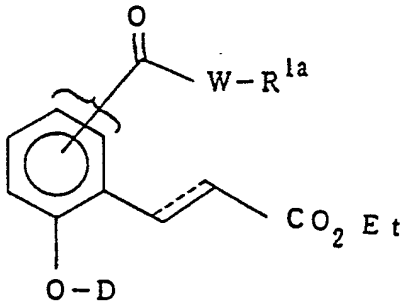
(XVI)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



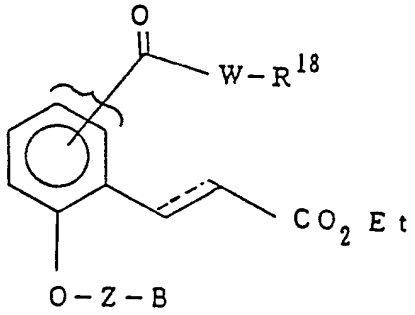
(XVII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



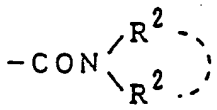
(XVIII)

wherein all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:

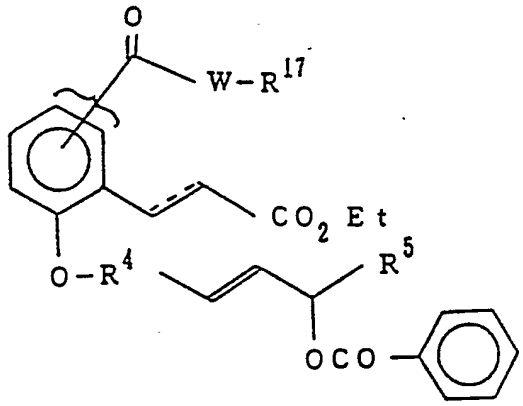


(XIX)

wherein R^{18} is
i) $-CO_2Et$,
ii) the group shown by



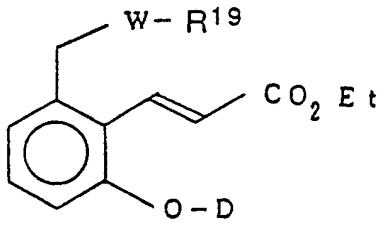
or
iii) $-CH_2OH$; and
the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



(XX)

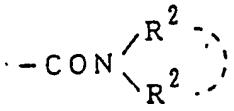
wherein, all of the symbols are the same meanings as described hereinbefore;,

the compound of the formula:

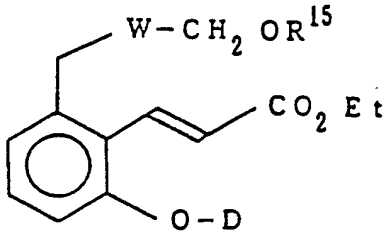


(XXI)

wherein R^{19} is
i) the group shown by

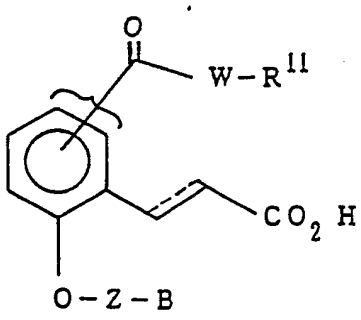


or
ii) $-CO_2Et$; and
the other symbols are the same meanings as described hereinbefore; or
the compound of the formula:



(XXII)

wherein all of the symbols are the same meanings as described hereinbefore;
with using an alkali (sodium hydroxide etc.) in an inert organic solvent (methanol, tetrahydrofuran etc.) or
3) reducing the compound of the formula:



(XIV)

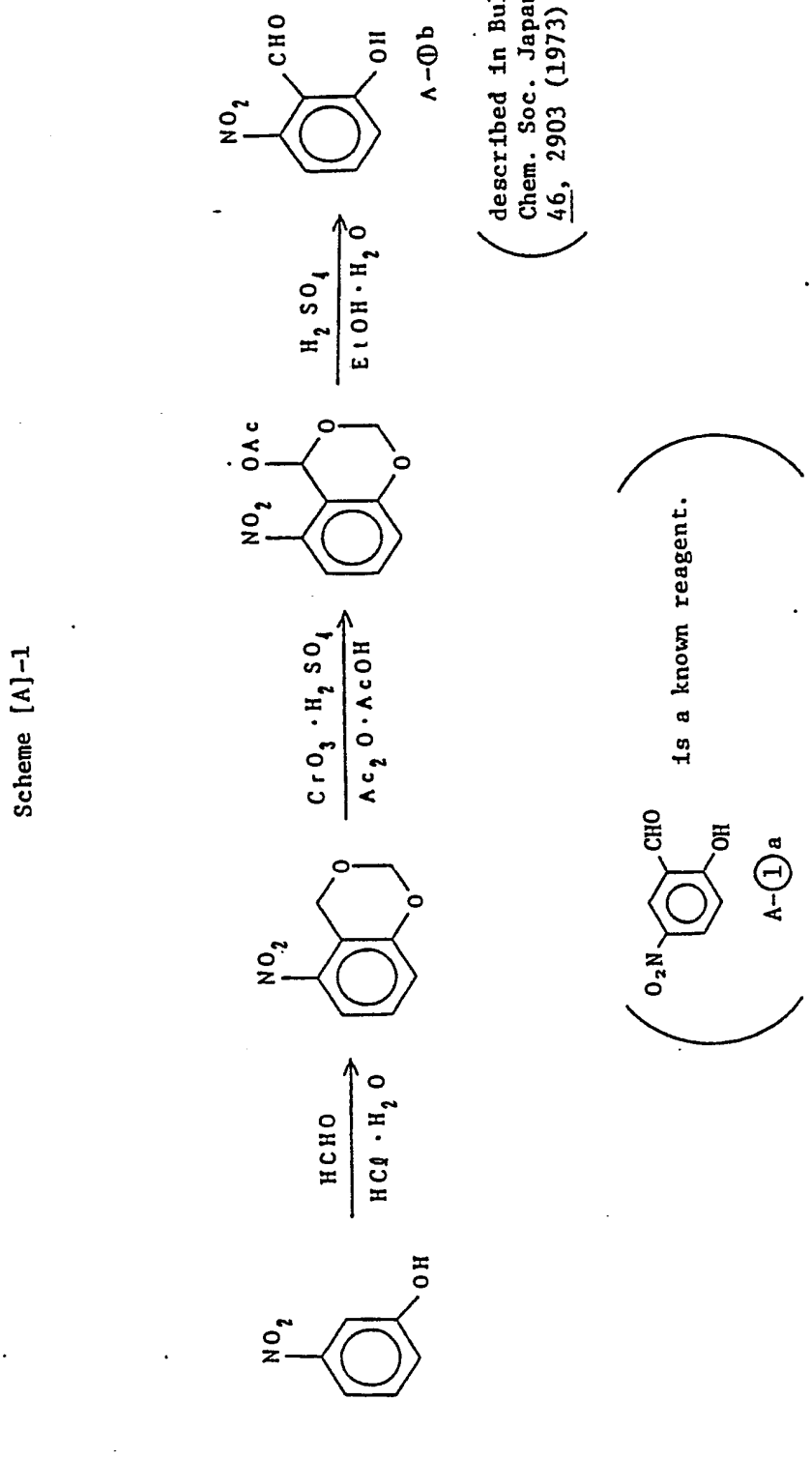
wherein all of the symbols are the same meanings as described hereinbefore;
with using reducing agent (sodium borohydride etc.) in an inert organic solvent (methanol etc.).

Process for the preparation of the intermediates

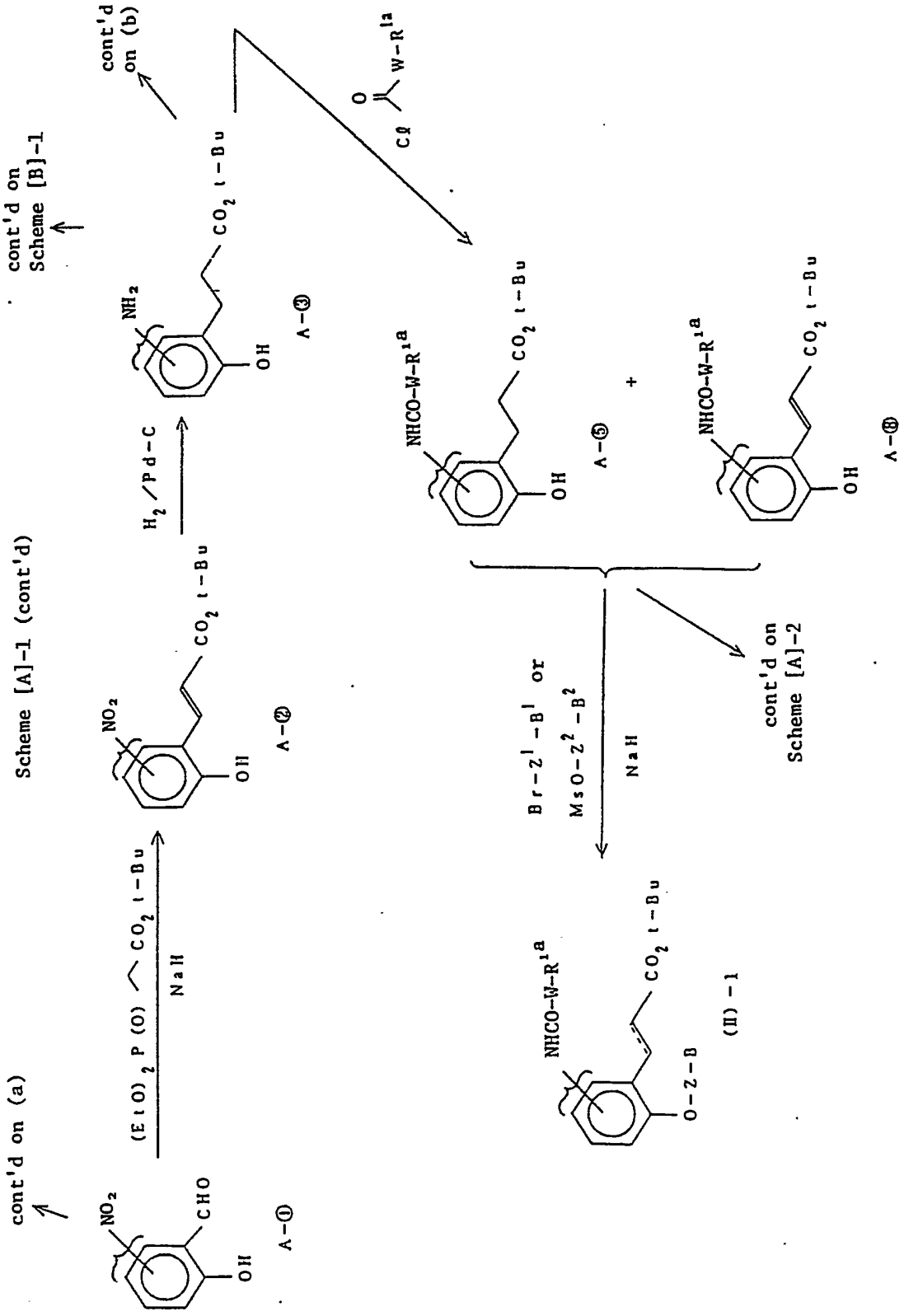
The compounds of the formulae (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI) and (XXII) may be prepared by the steps shown in the following

scheme [A], [B], [C], [D] and [E].

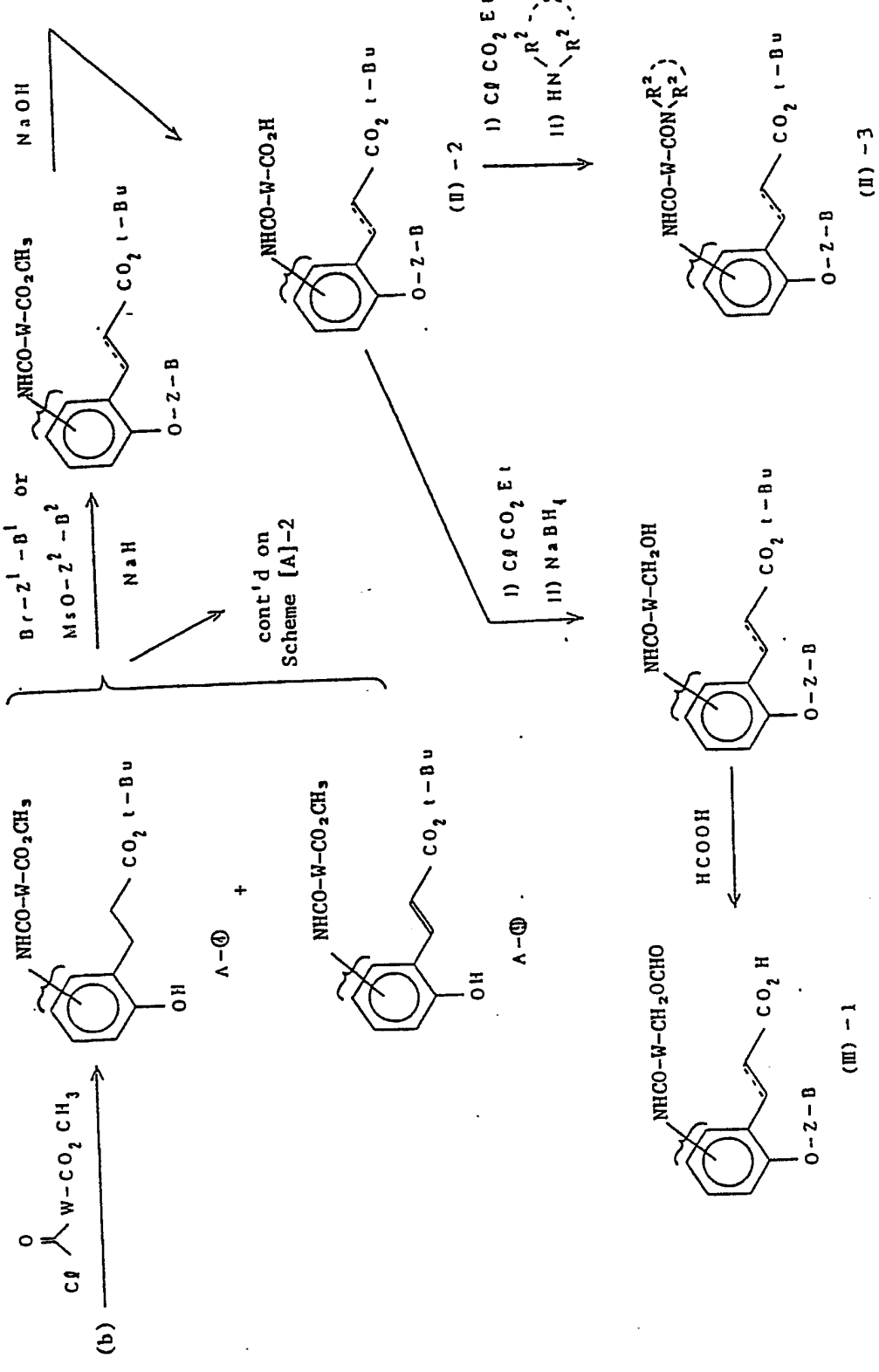
Scheme [A]-1


HCHO
HCℓ · H2O
CrO3 · H2SO4
Ac2O · AcOH
H2SO4
EtOH · H2O
described in Bull. Chem. Soc. Japan, 46, 2903 (1973)
is a known reagent.
A-①a
A-①b

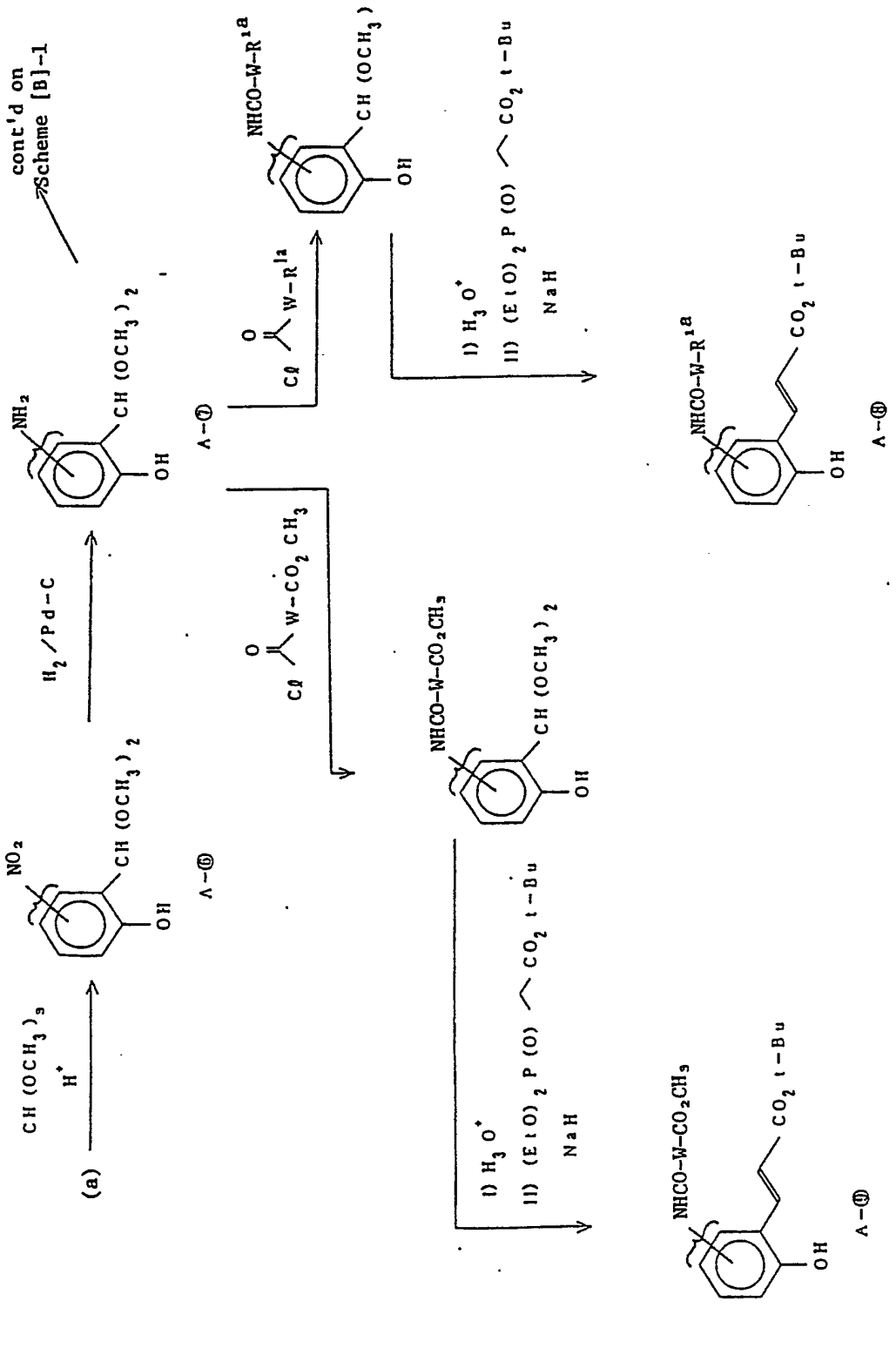
Scheme [A]-1 (cont'd)



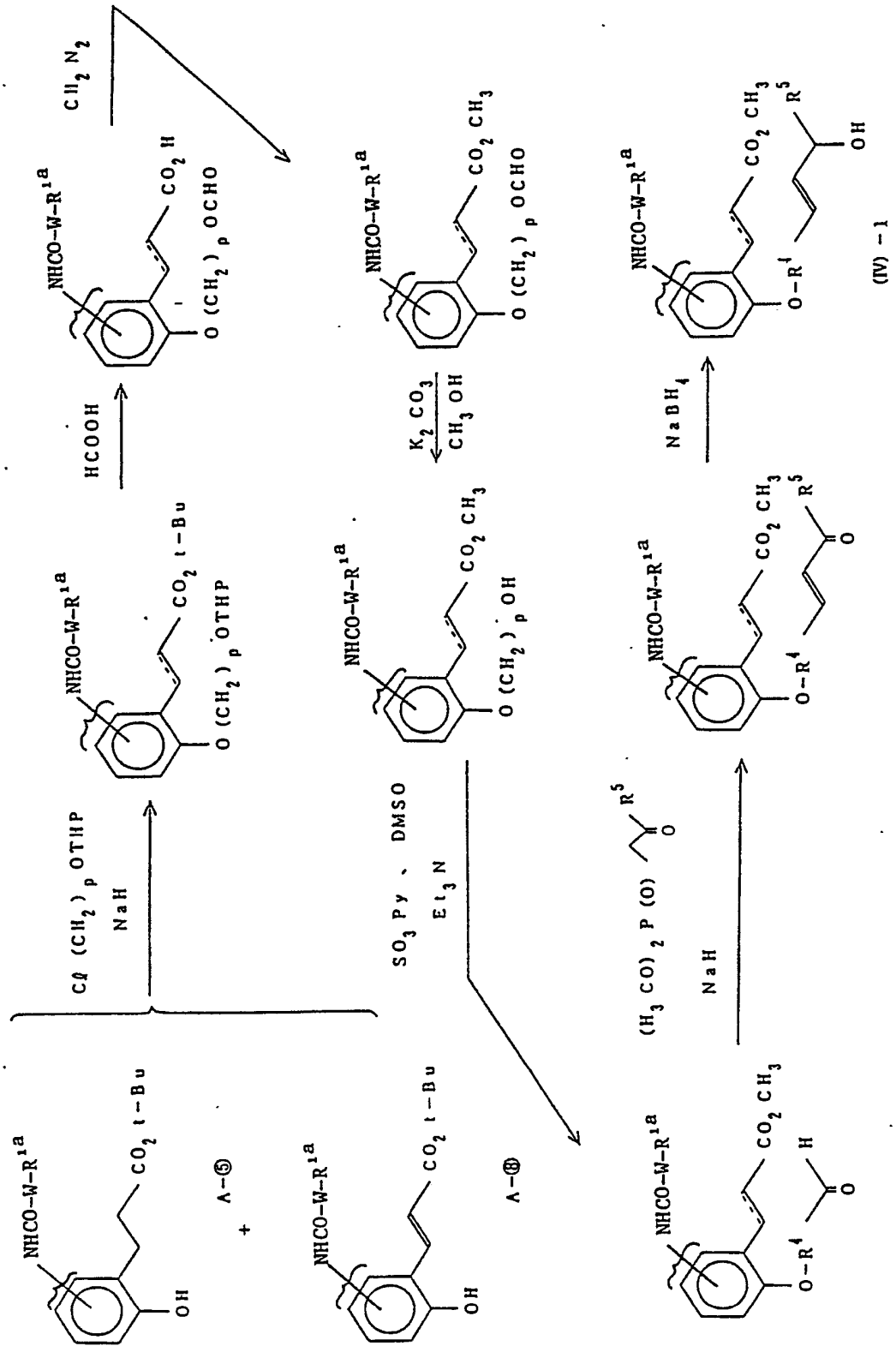
Scheme [A]-1 (cont'd)



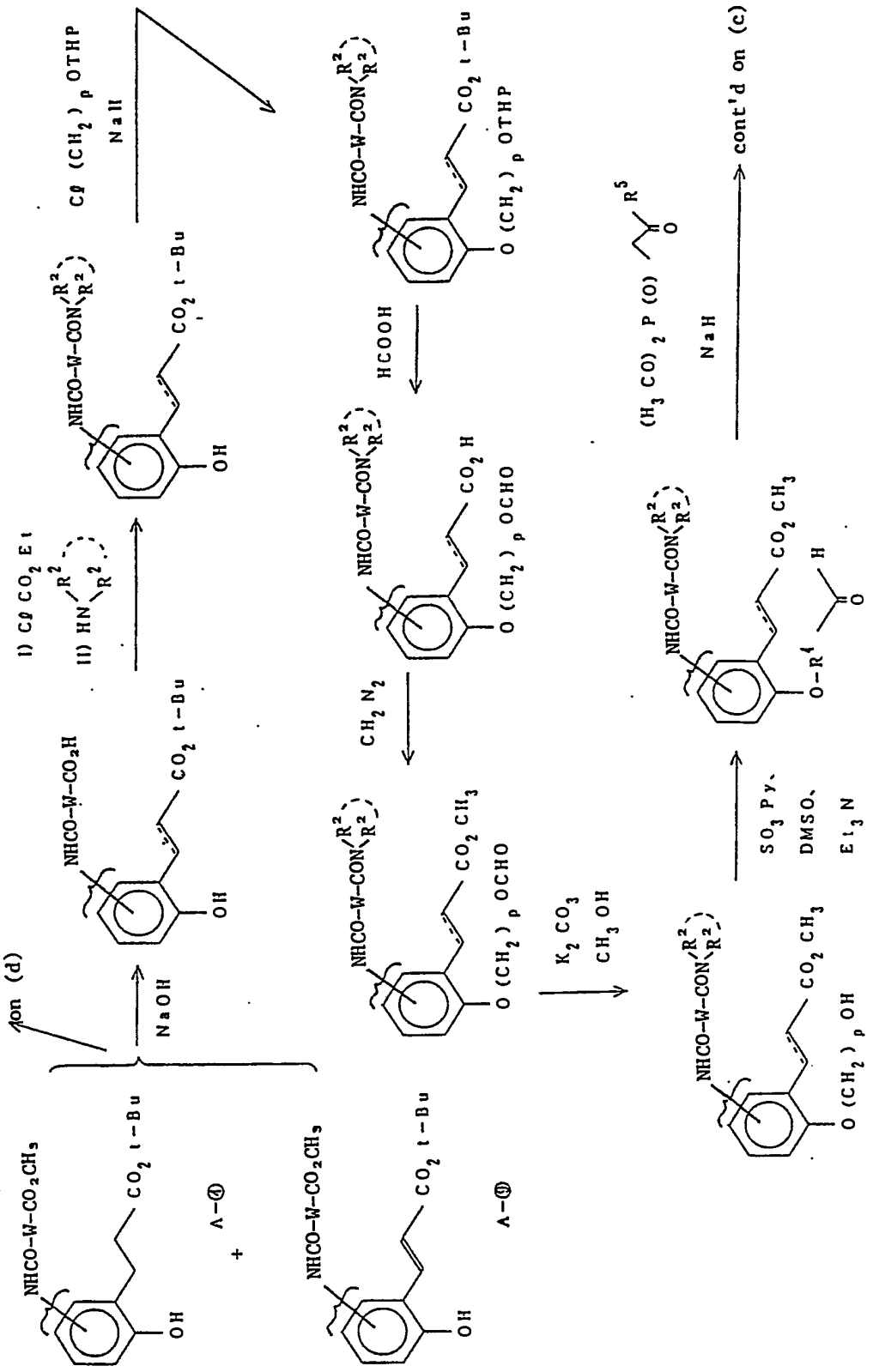
Scheme [A]-1 (cont'd)



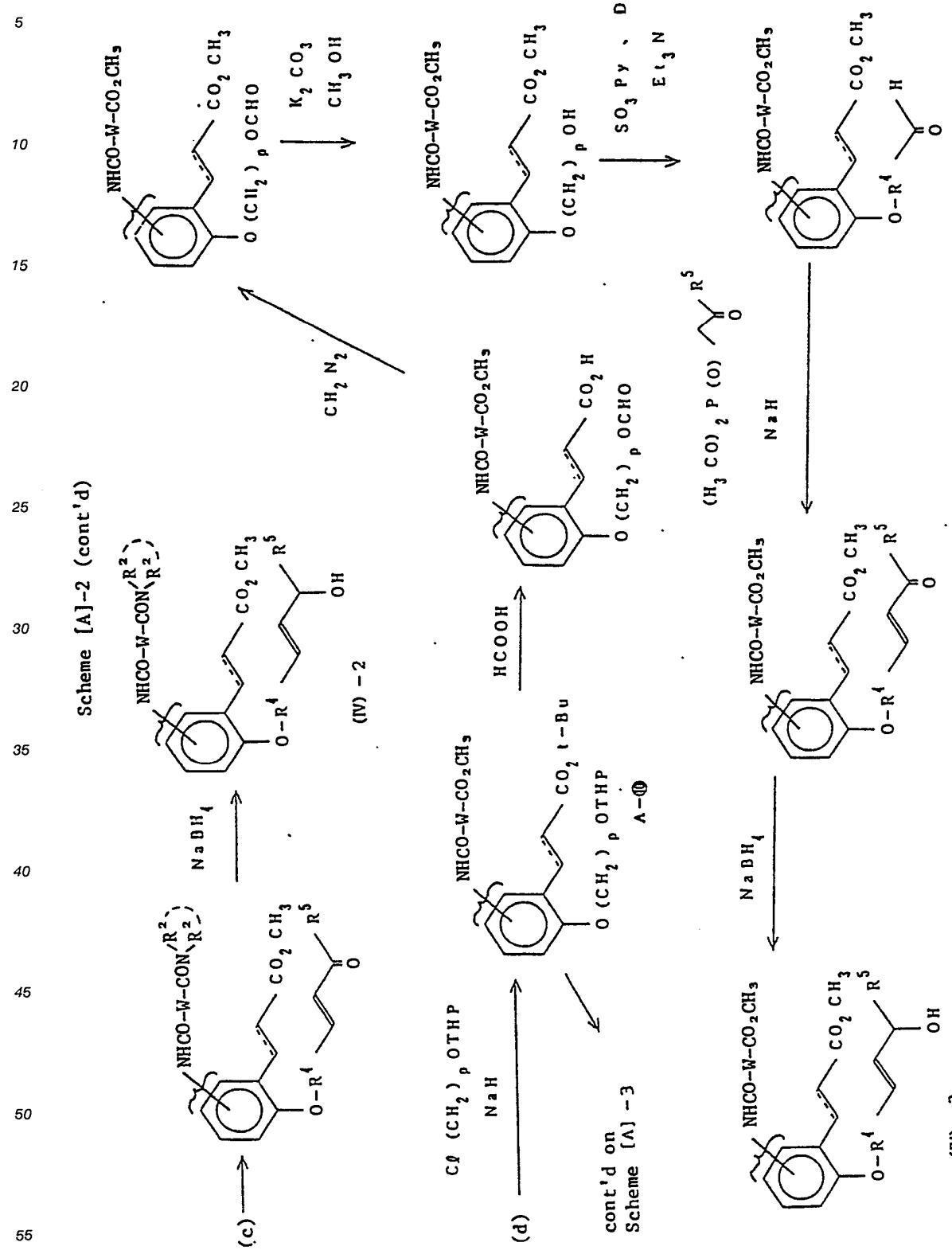
Scheme [A]-2


NHCO-W-R1a
CO2 t-Bu
O (CH2)p OTHP
NaH
Cl (CH2)p OTHP
A-⑤
+
A-⑥
SO3 Py ・ DMSO
Et3N
HCOOH
CH2N2
O (CH2)p OCHO
CO2H
K2CO3
CH3OH
CO2CH3
O (CH2)p OH
NaBH4
(H3CO)2P(O)
O-R4
R5
OH
(IV)-1

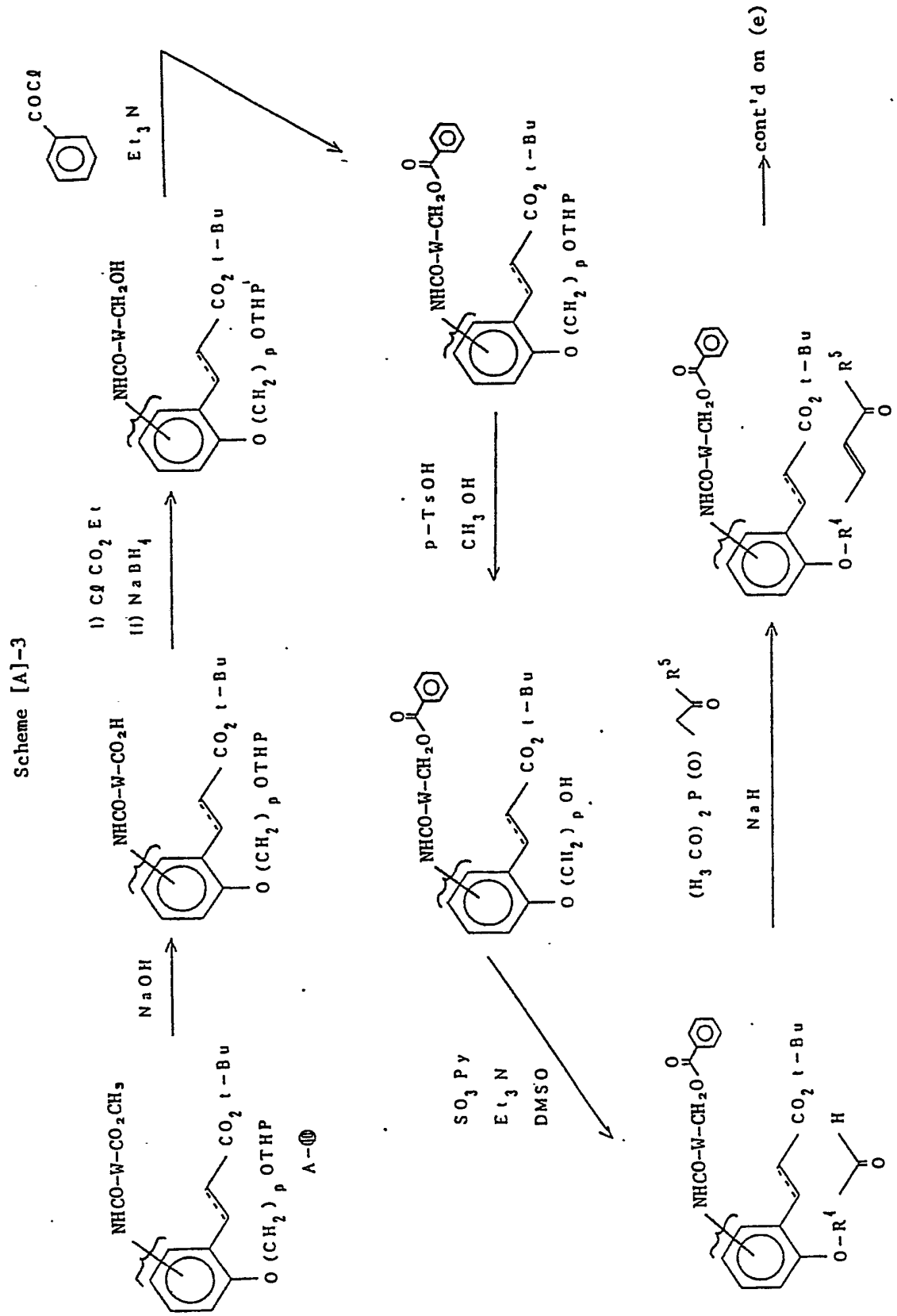
Scheme [A]-2 (cont'd)



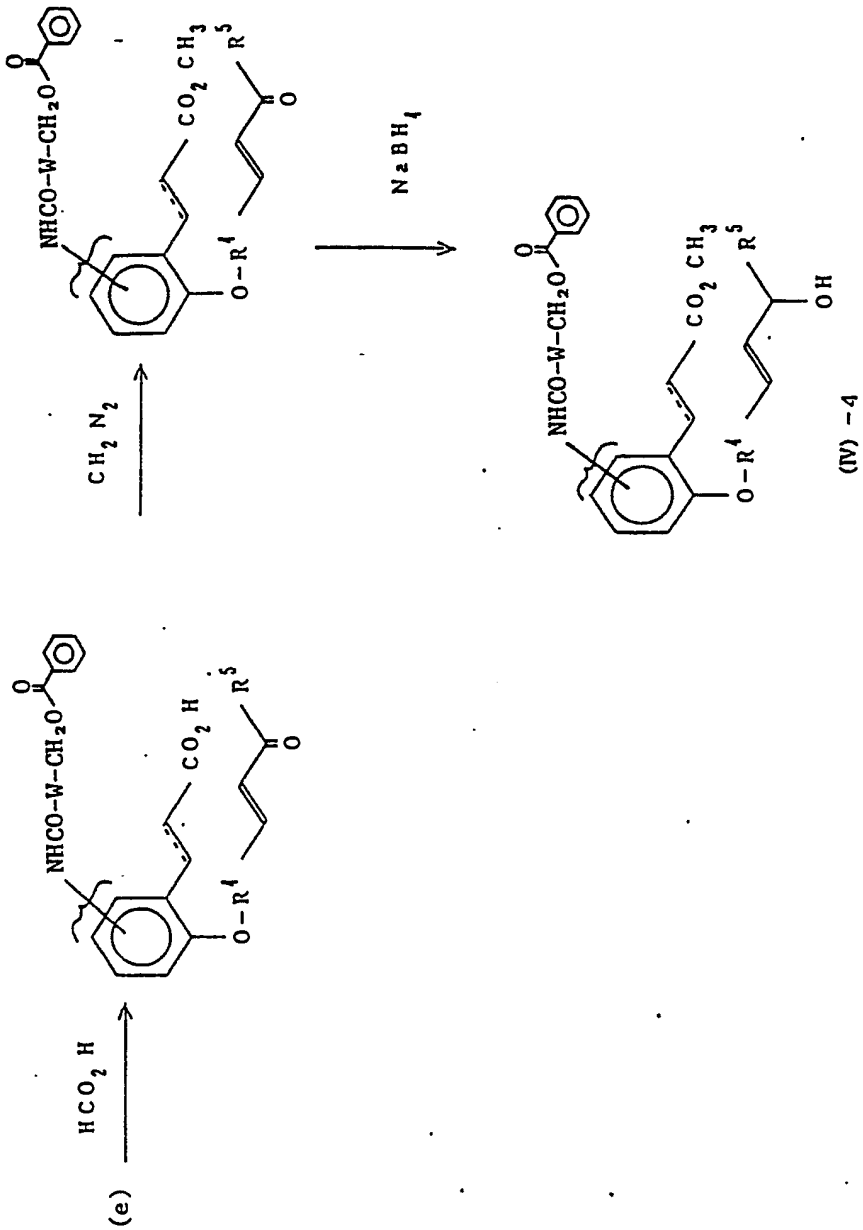
Scheme [A]-2 (cont'd)



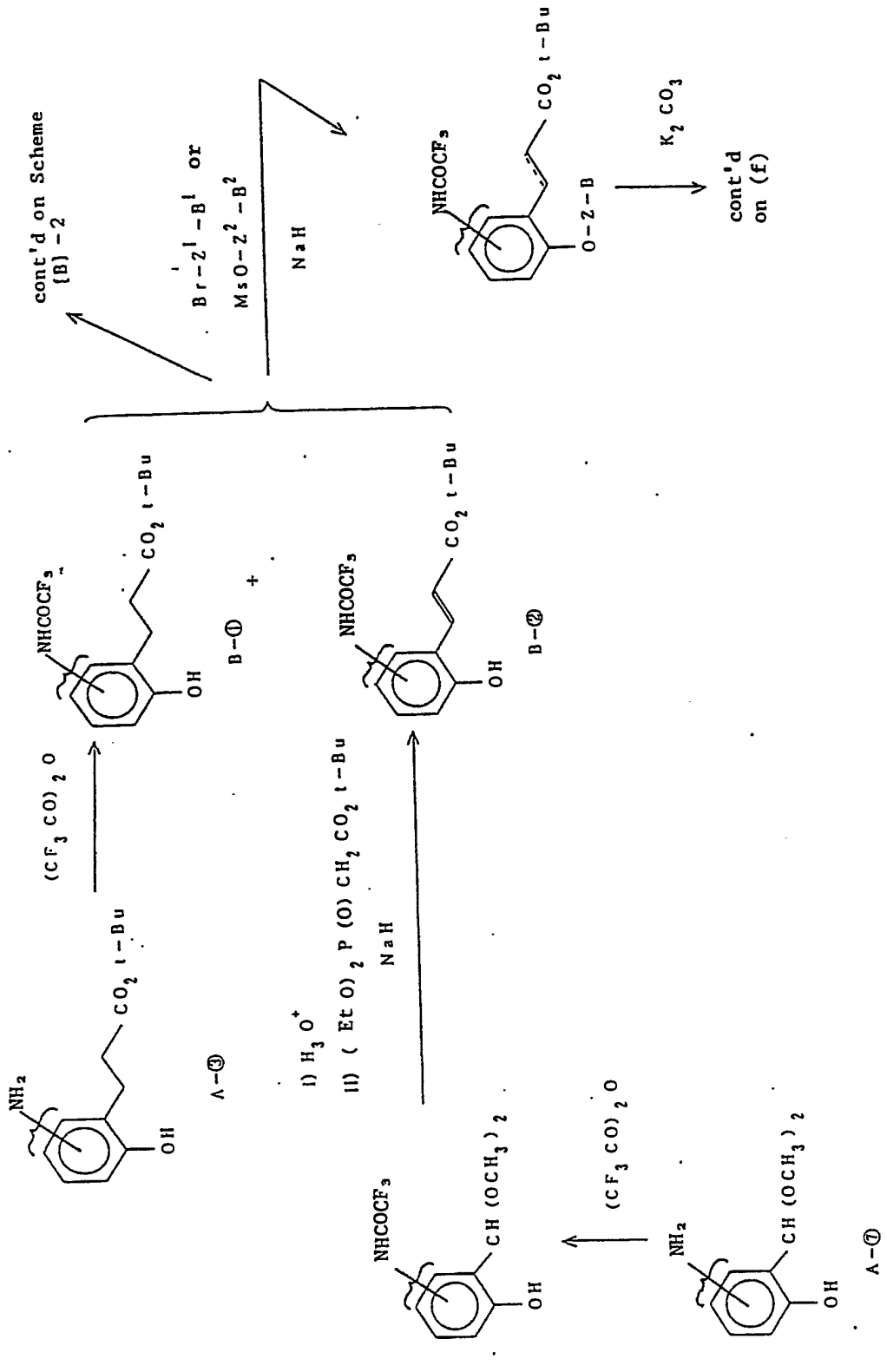
Scheme [A]-3


NHCO-W-CO2CH3
CO2 t-Bu
O (CH2)p OTHP
A-(iii)
NaOH
NHCO-W-CO2H
CO2 t-Bu
O (CH2)p OTHP
1) Cl CO2 Et
ii) NaBH4
NHCO-W-CH2OH
CO2 t-Bu
O (CH2)p OTHP'
Et3N
COCl
SO3 Py
Et3N
DMSO
NHCO-W-CH2O
CO2 t-Bu
O (CH2)p OH
p-TsOH
CH3OH
NHCO-W-CH2O
CO2 t-Bu
O (CH2)p OTHP
(H3CO)2P(O)
R5
O
NaH
NHCO-W-CH2O
CO2 t-Bu
O-R4
R5
O
NHCO-W-CH2O
CO2 t-Bu
O-R4
H
O
cont'd on (e)

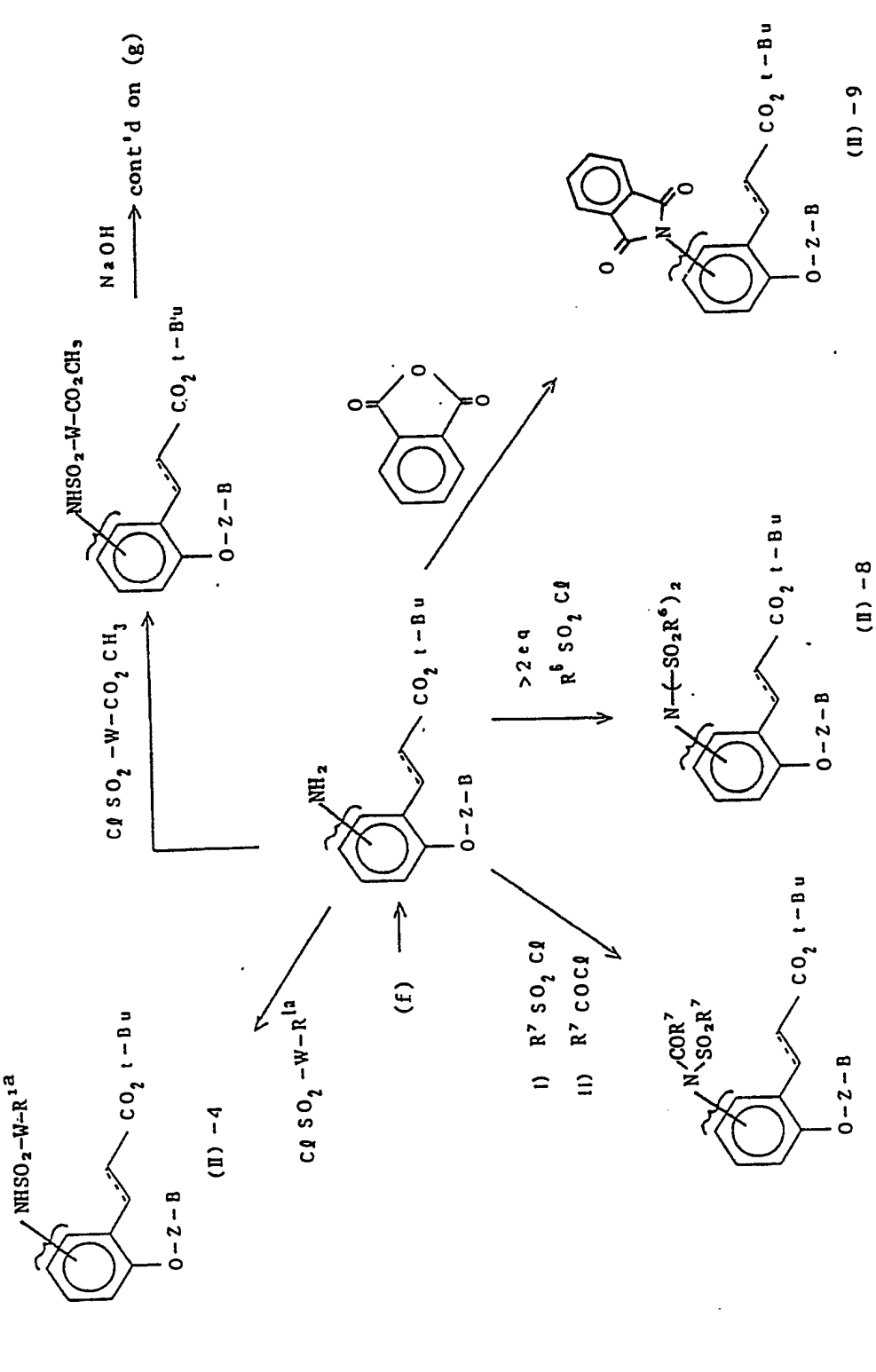
Scheme [A]-3 (cont'd)



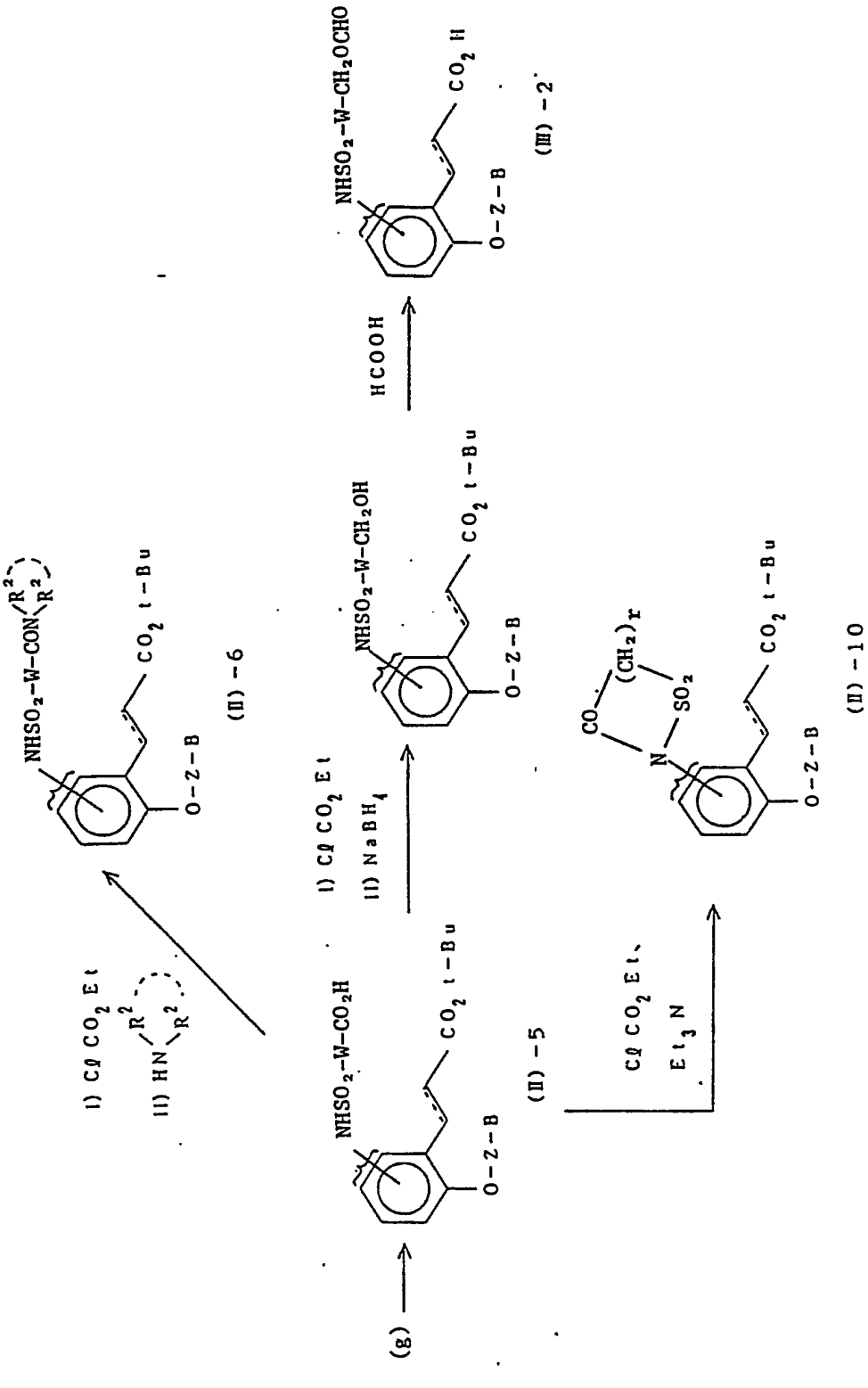
Scheme [B]-1


A-①
A-③
B-①
B-②
cont'd on Scheme (B)-2
Br-Z¹-B¹ or MsO-Z²-B²
NaH
K₂CO₃
cont'd on (f)
(CF₃CO)₂O
1) H₃O⁺
2) (EtO)₂P(O)CH₂CO₂t-Bu
NaH
NHCOCF₃
NH₂
OH
CO₂t-Bu
CH(OCH₃)₂
O-Z-B

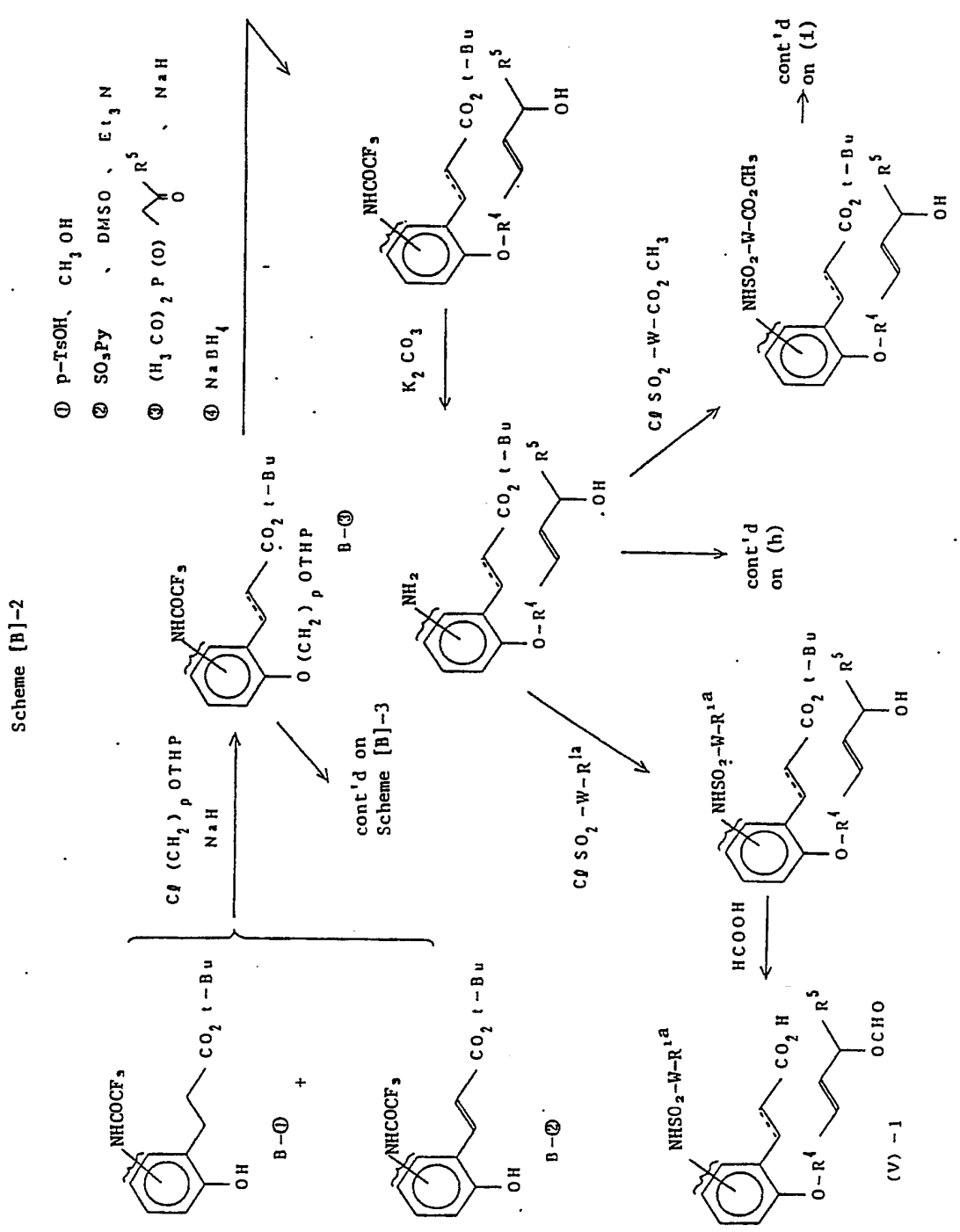
Scheme [B]-1 (cont'd)



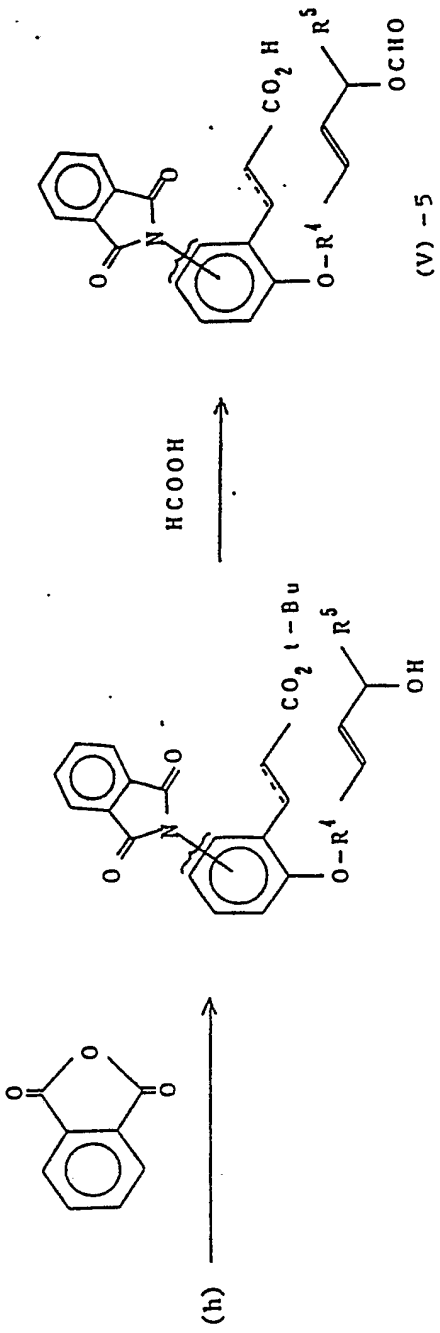
Scheme [B]-1 (cont'd)



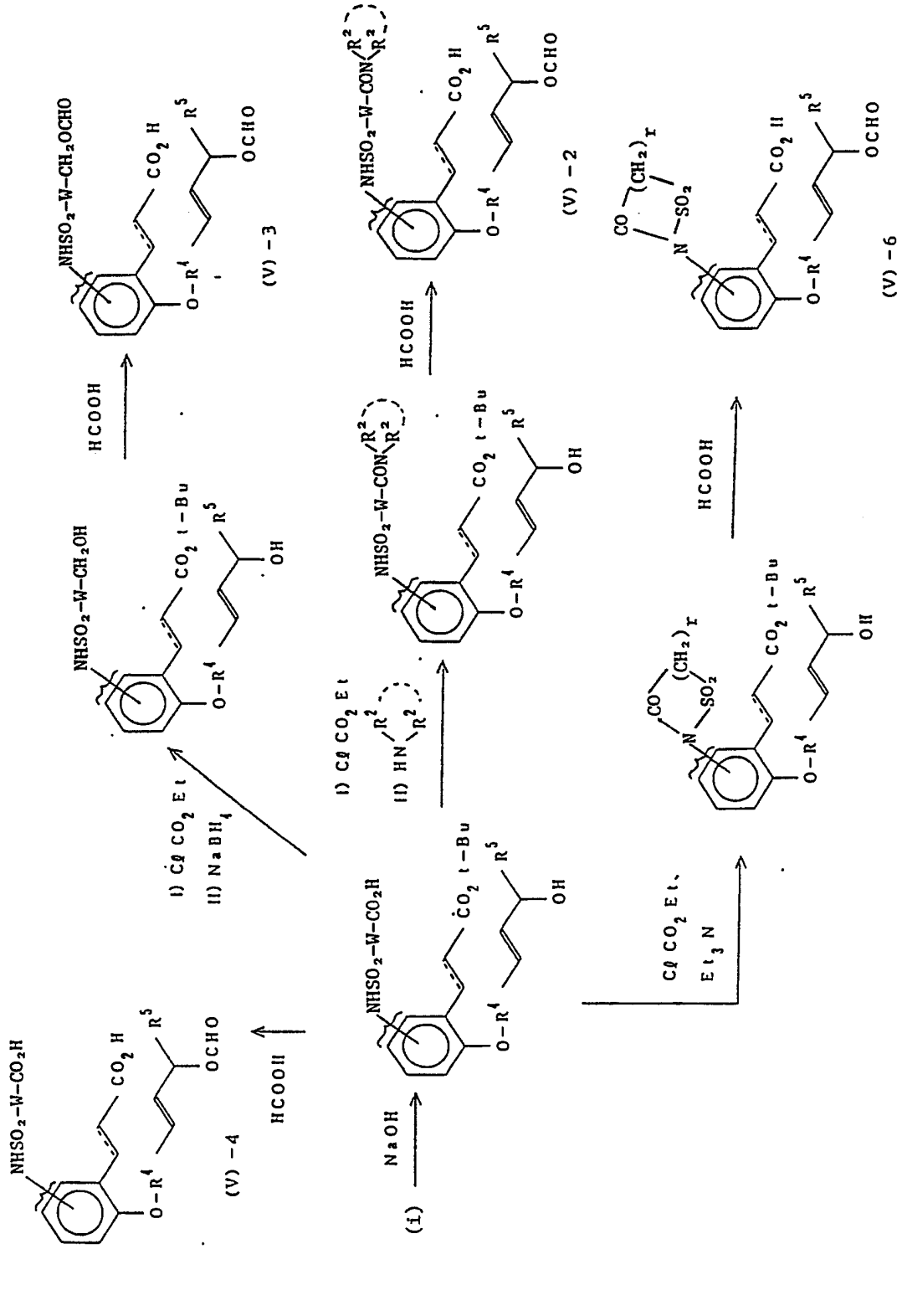
Scheme [B]-2


① p-TsOH, CH3OH
② SO3Py, DMSO, Et3N
③ (H3CO)2P(O)CH(R5)C(=O)R5, NaH
④ NaBH4
K2CO3
Cℓ(CH2)pOTHP
NaH
cont'd on Scheme [B]-3
Cℓ SO2-W-R1a
Cℓ SO2-W-CO2CH3
cont'd on (h)
cont'd on (i)
HCOOH
B-①
B-②
B-③
(V)-1
NHCOCF3
NH2
NHSO2-W-R1a
NHSO2-W-CO2CH3
CO2t-Bu
OH
OCHO
O-R4
O(CH2)pOTHP
R5

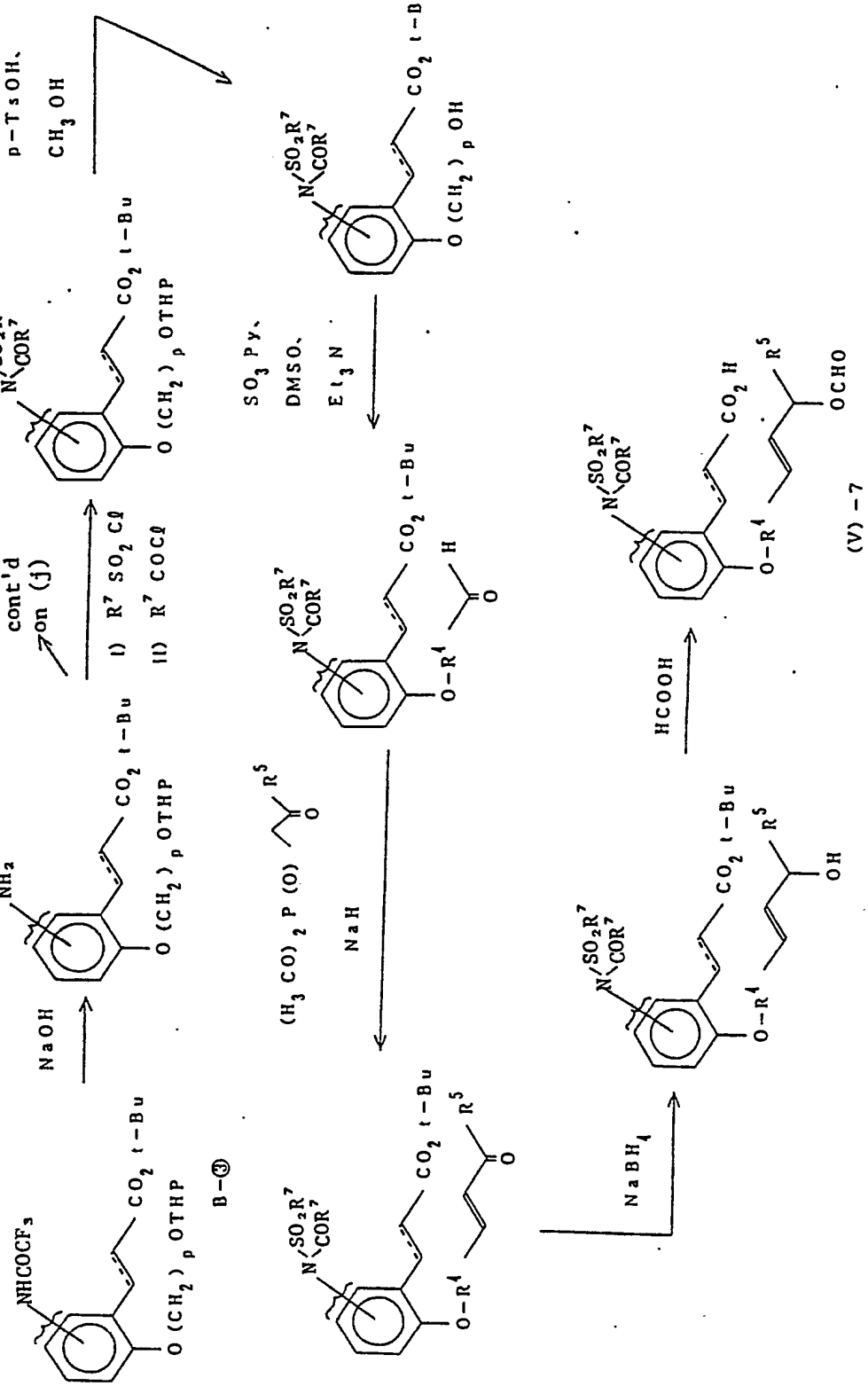
Scheme [B]-2 (cont'd)



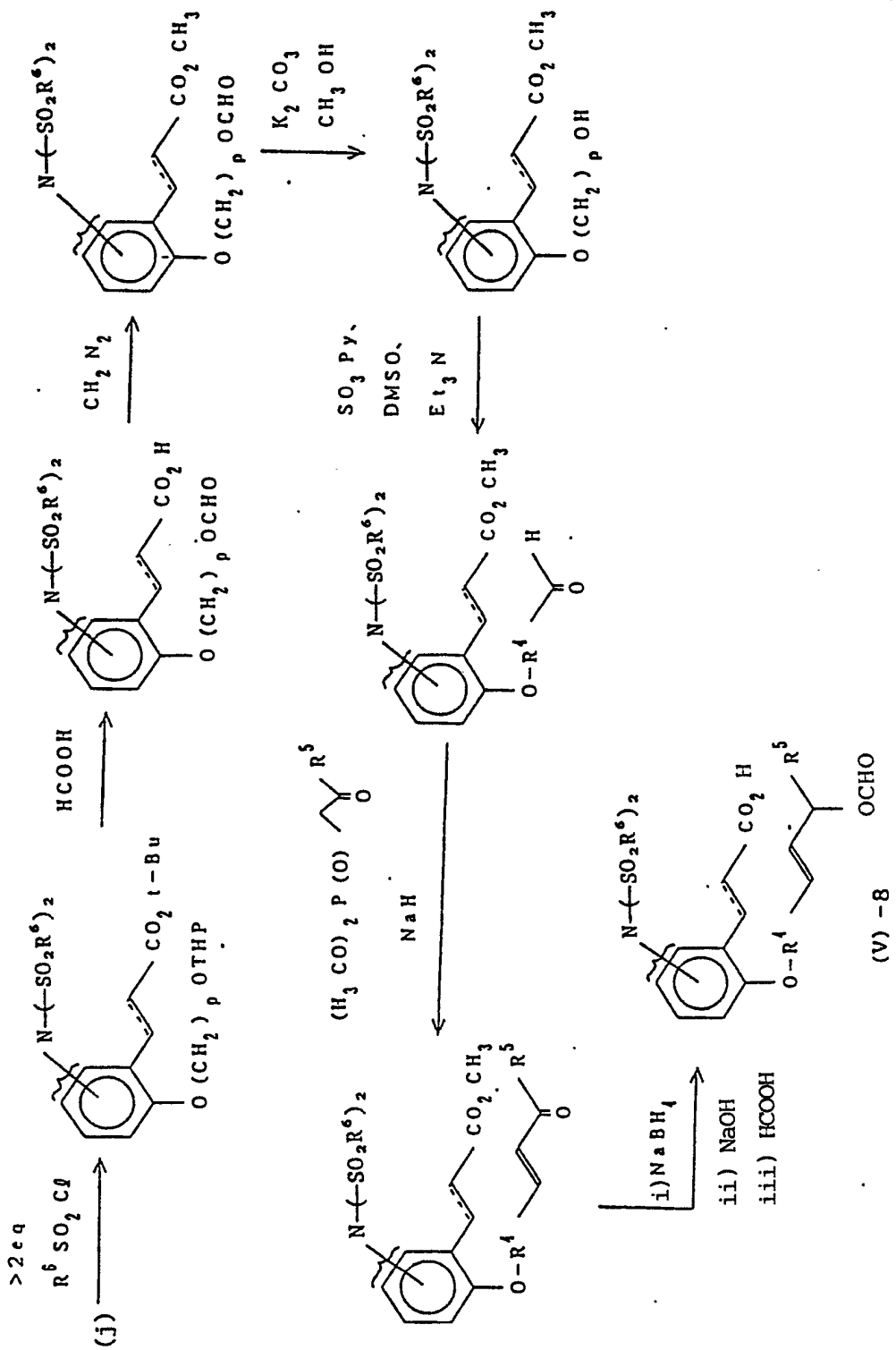
Scheme [B]-2 (cont'd)

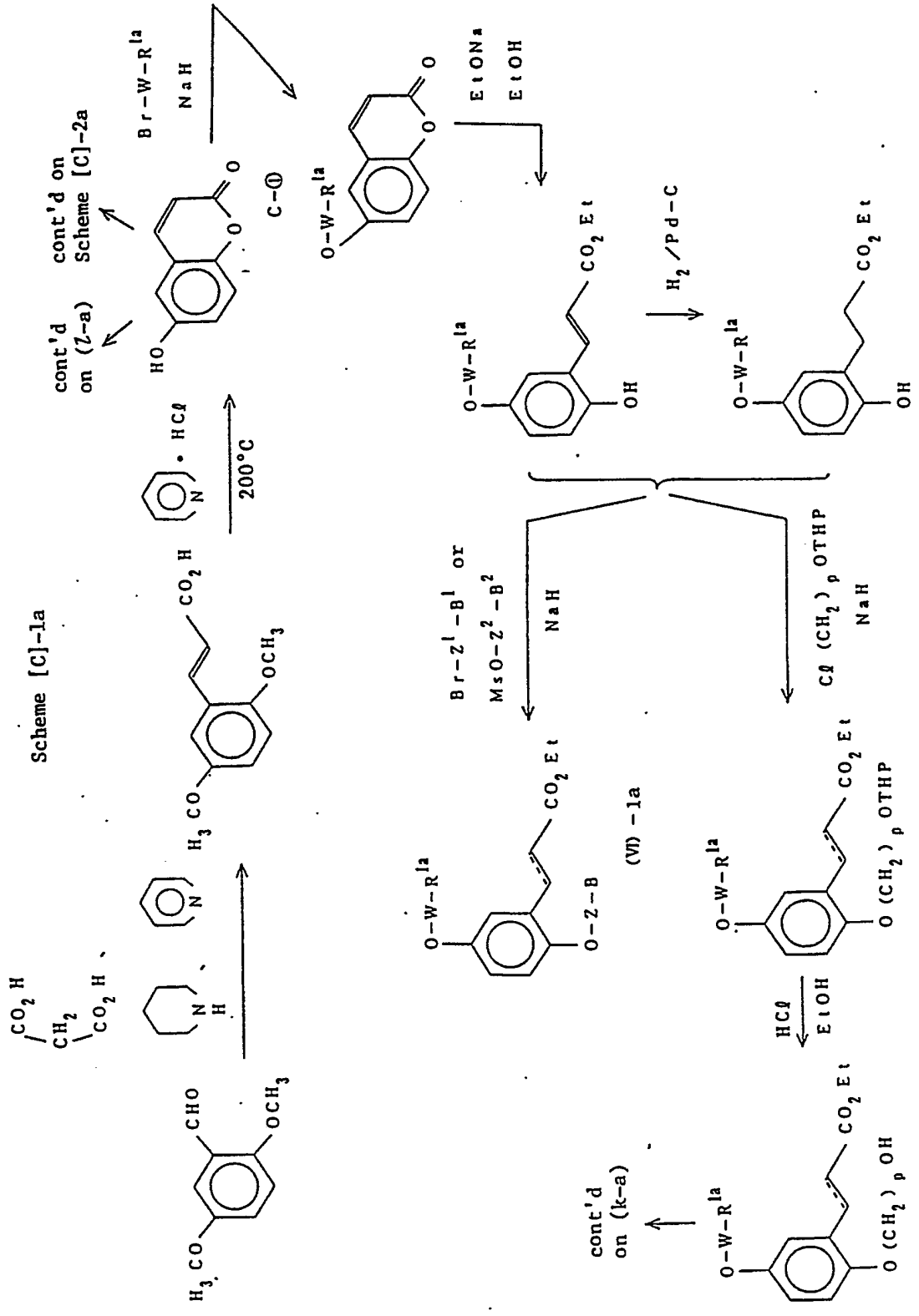


Scheme [B]-3

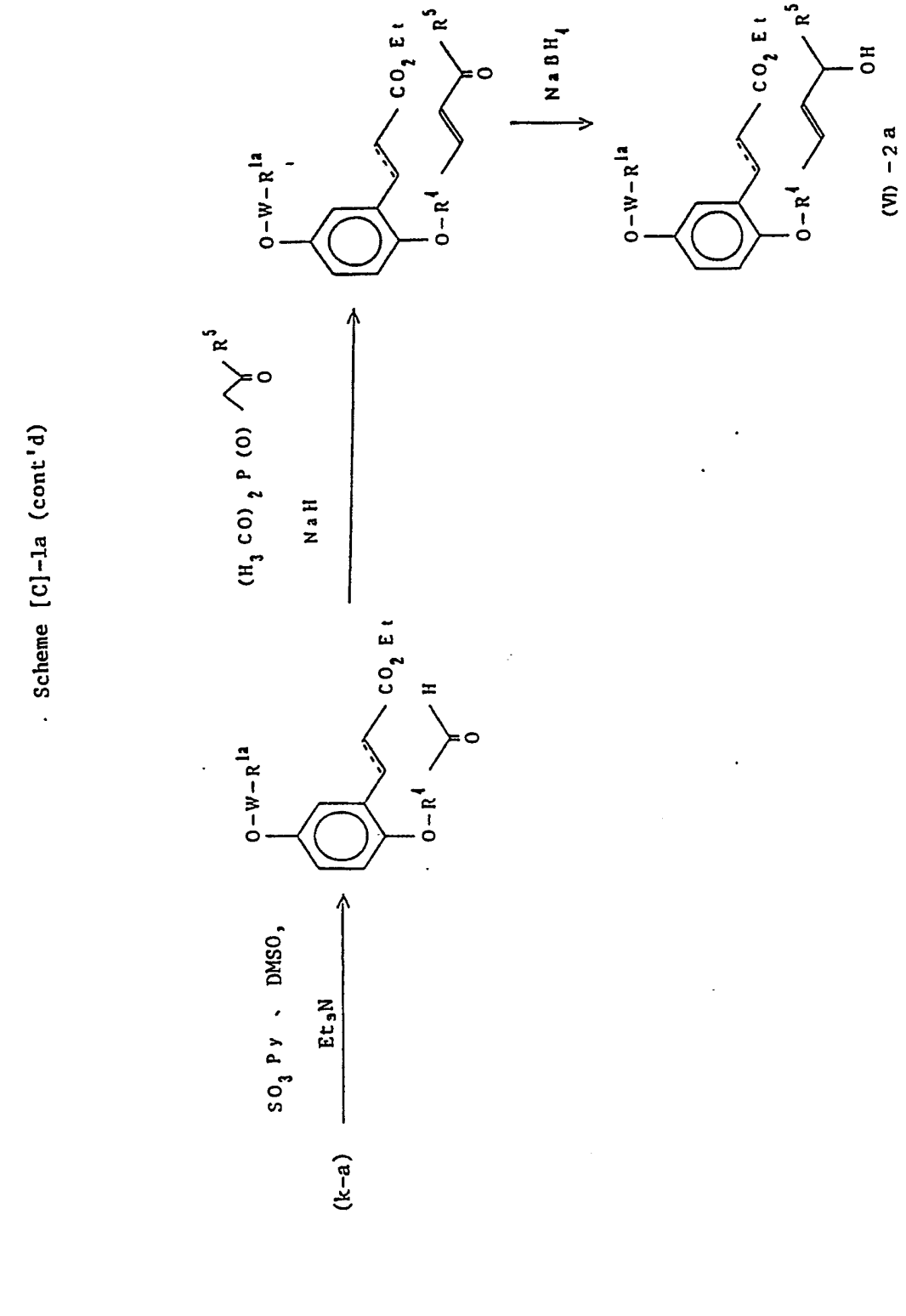

NHCOCF3
CO2 t-Bu
O(CH2)p OTHP
B-③
NaOH
NH2
CO2 t-Bu
O(CH2)p OTHP
cont'd on (j)
I) R7SO2Cℓ
II) R7COCℓ
N(SO2R7)(COR7)
CO2 t-Bu
O(CH2)p OTHP
p-TsOH.
CH3OH
N(SO2R7)(COR7)
CO2 t-Bu
O(CH2)p OH
SO3Py.
DMSO.
Et3N
(H3CO)2P(O)
R5
O
NaH
N(SO2R7)(COR7)
CO2 t-Bu
R5
O
O-R4
NaBH4
N(SO2R7)(COR7)
CO2 t-Bu
R5
OH
O-R4
HCOOH
N(SO2R7)(COR7)
CO2H
R5
OCHO
O-R4
(V)-7

Scheme [B]-3 (cont'd)

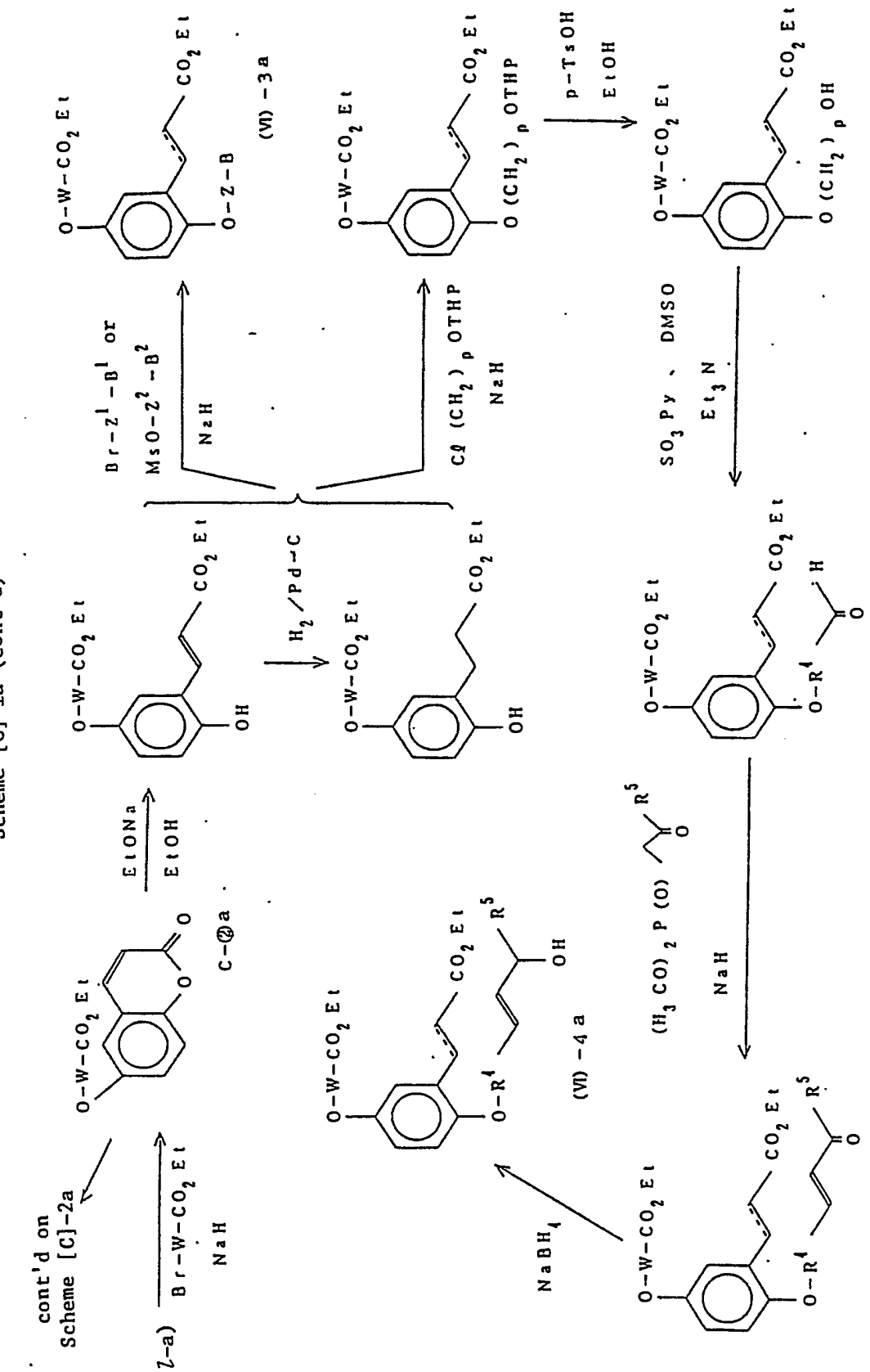



Scheme [C]-1a
cont'd on Scheme [C]-2a
cont'd on (Z-a)
C-①
200°C
NaH
EtONa
EtOH
H2/Pd-C
HCℓ
cont'd on (k-a)
(VI)-1a

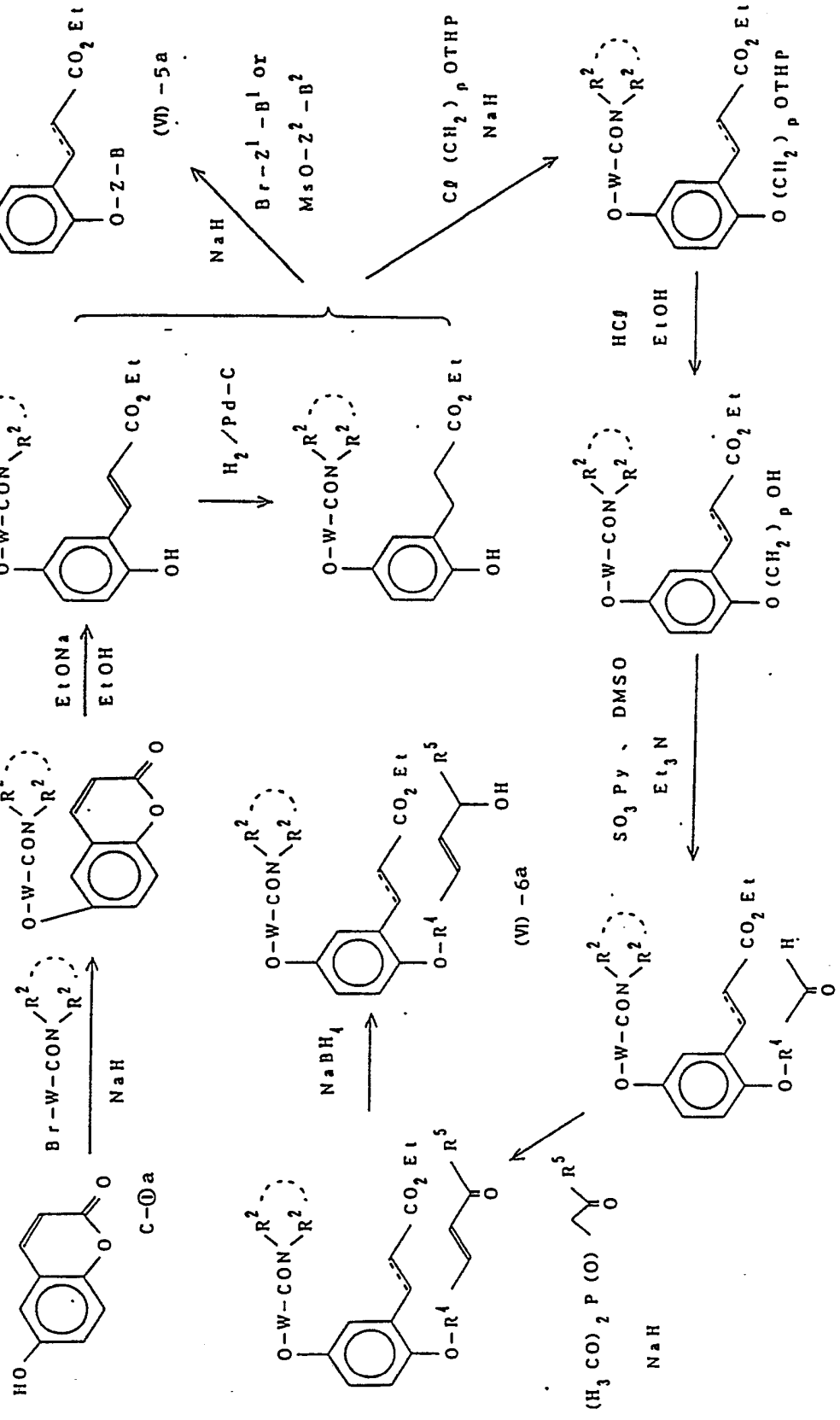
Scheme [C]-1a (cont'd)



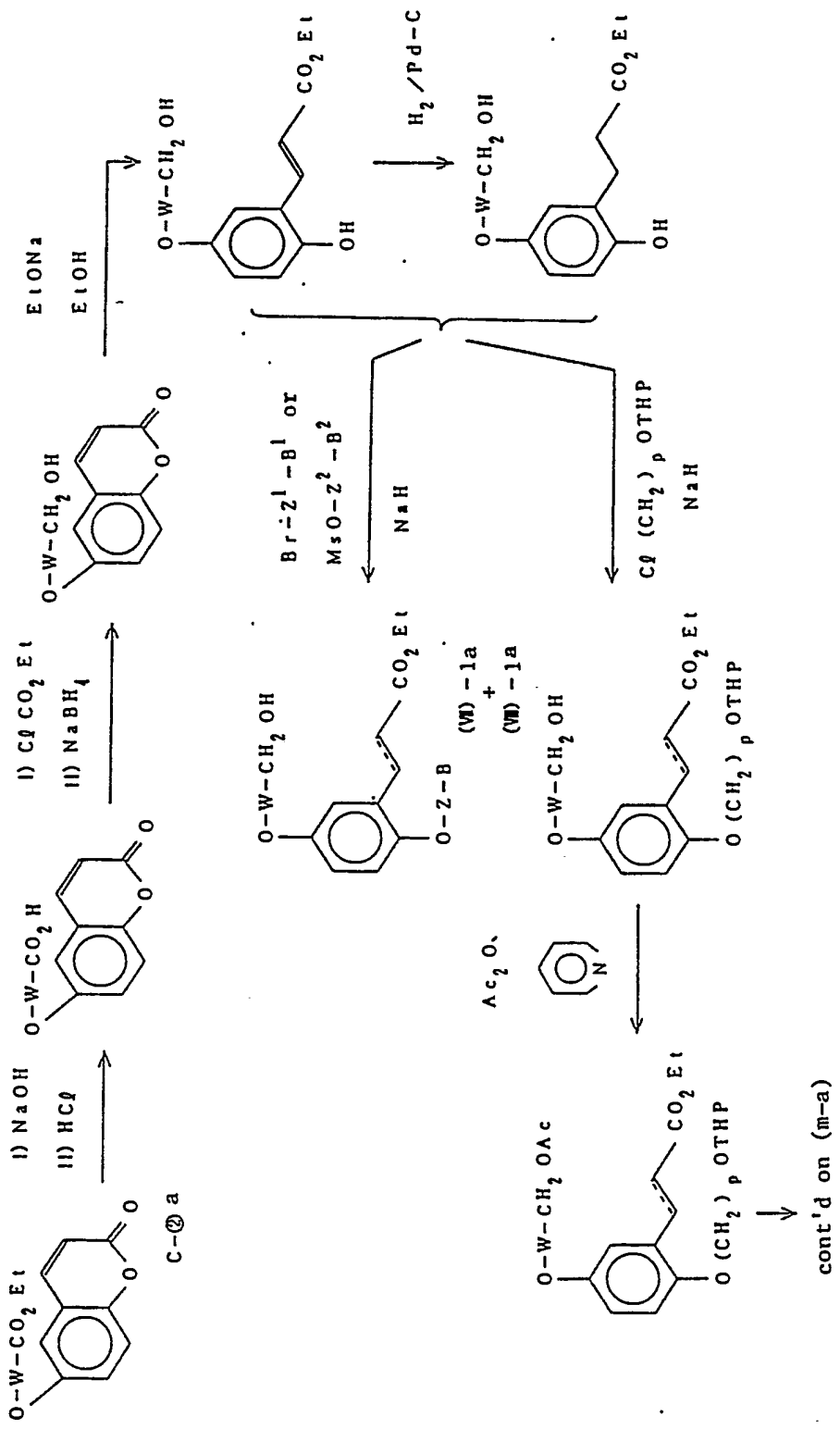
Scheme [C]-1a (cont'd)



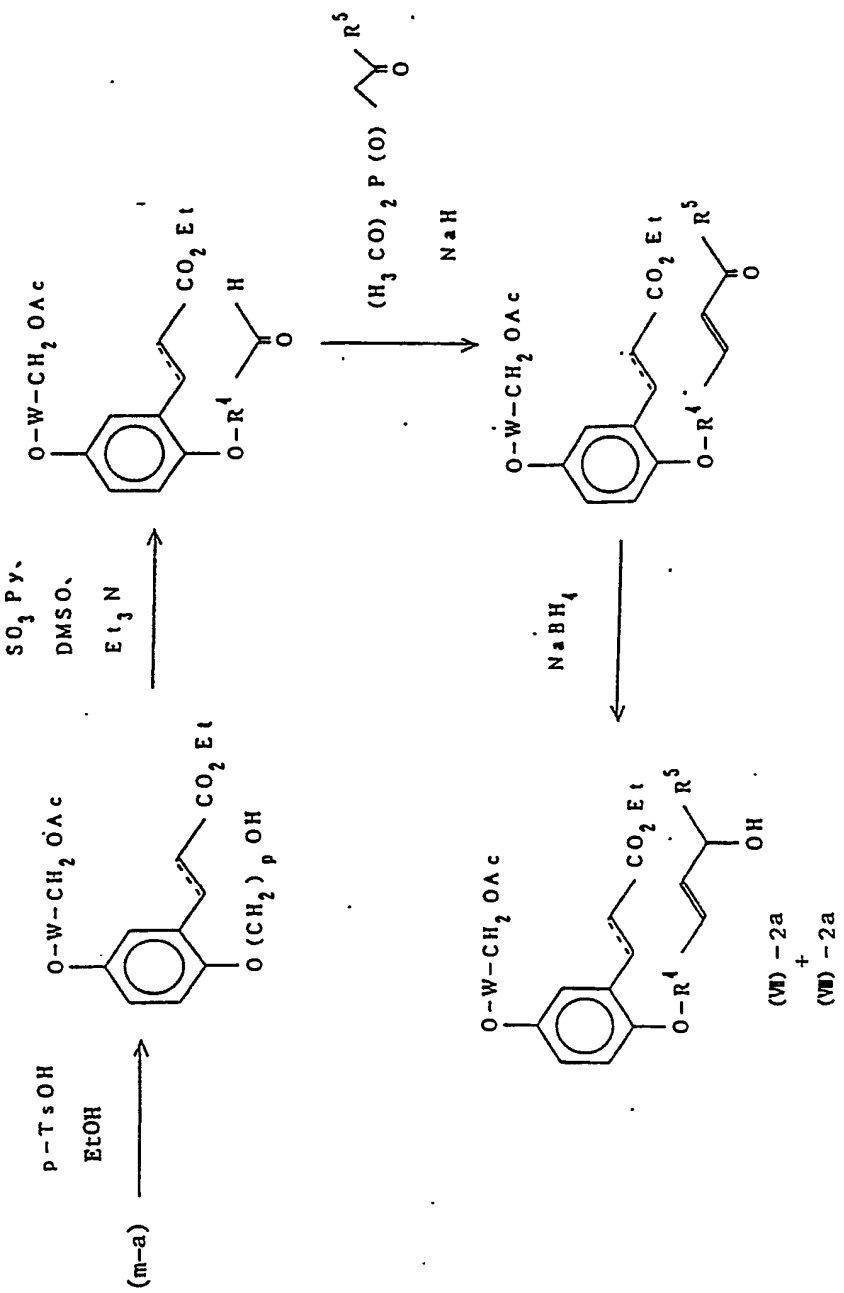
Scheme [C]-2a



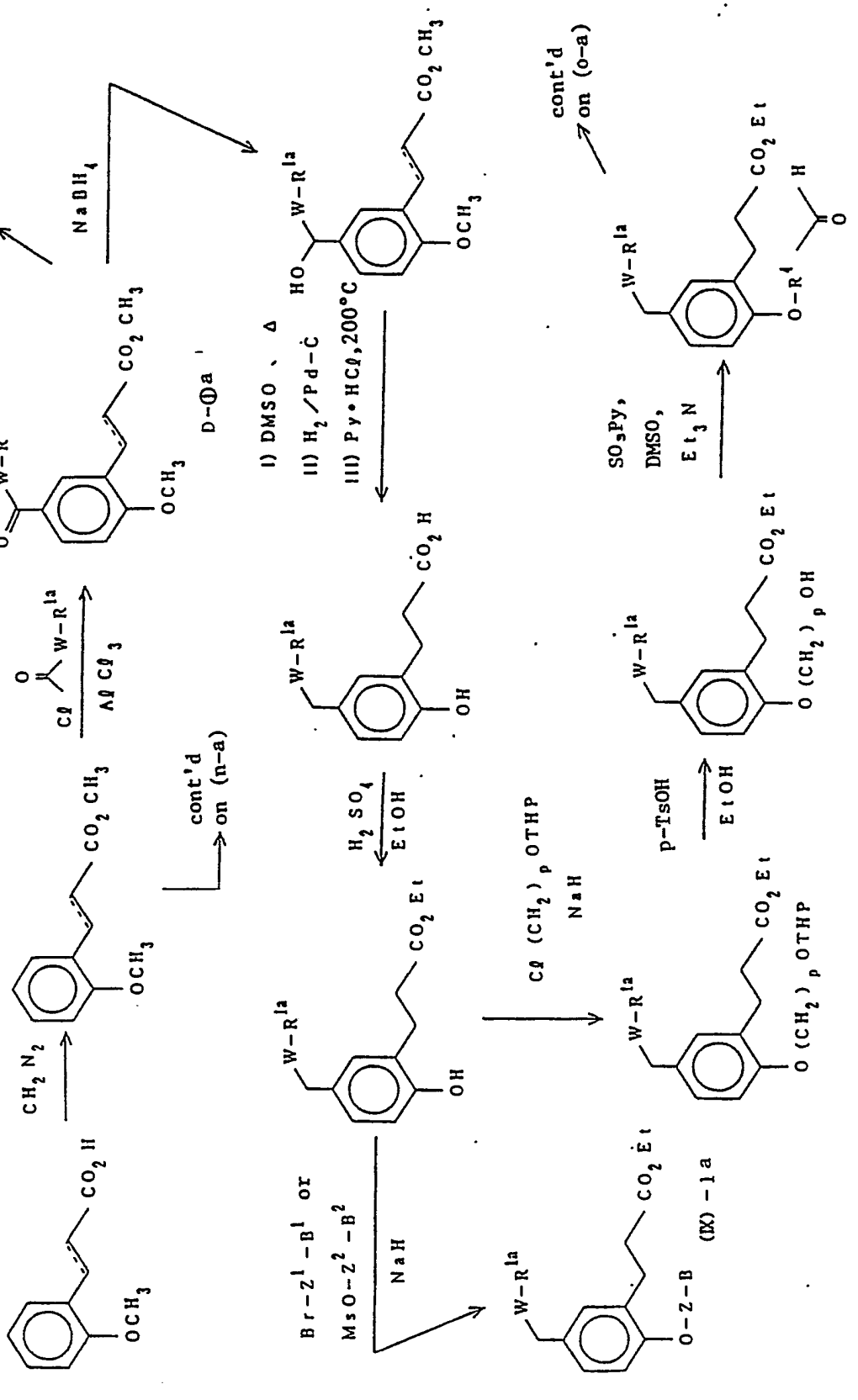
Scheme [C]-2a (cont'd)



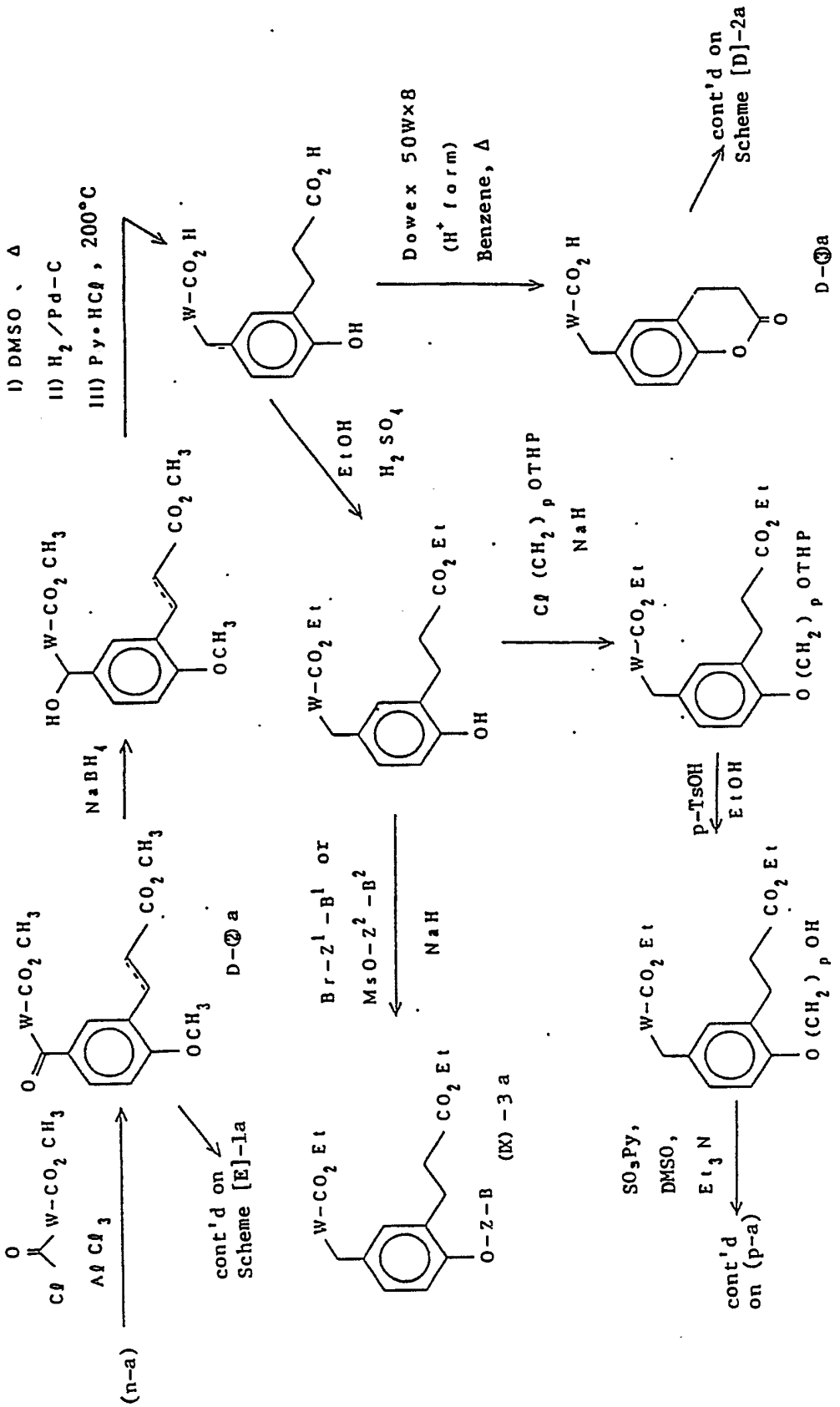
Scheme [C]-2a (cont'd)



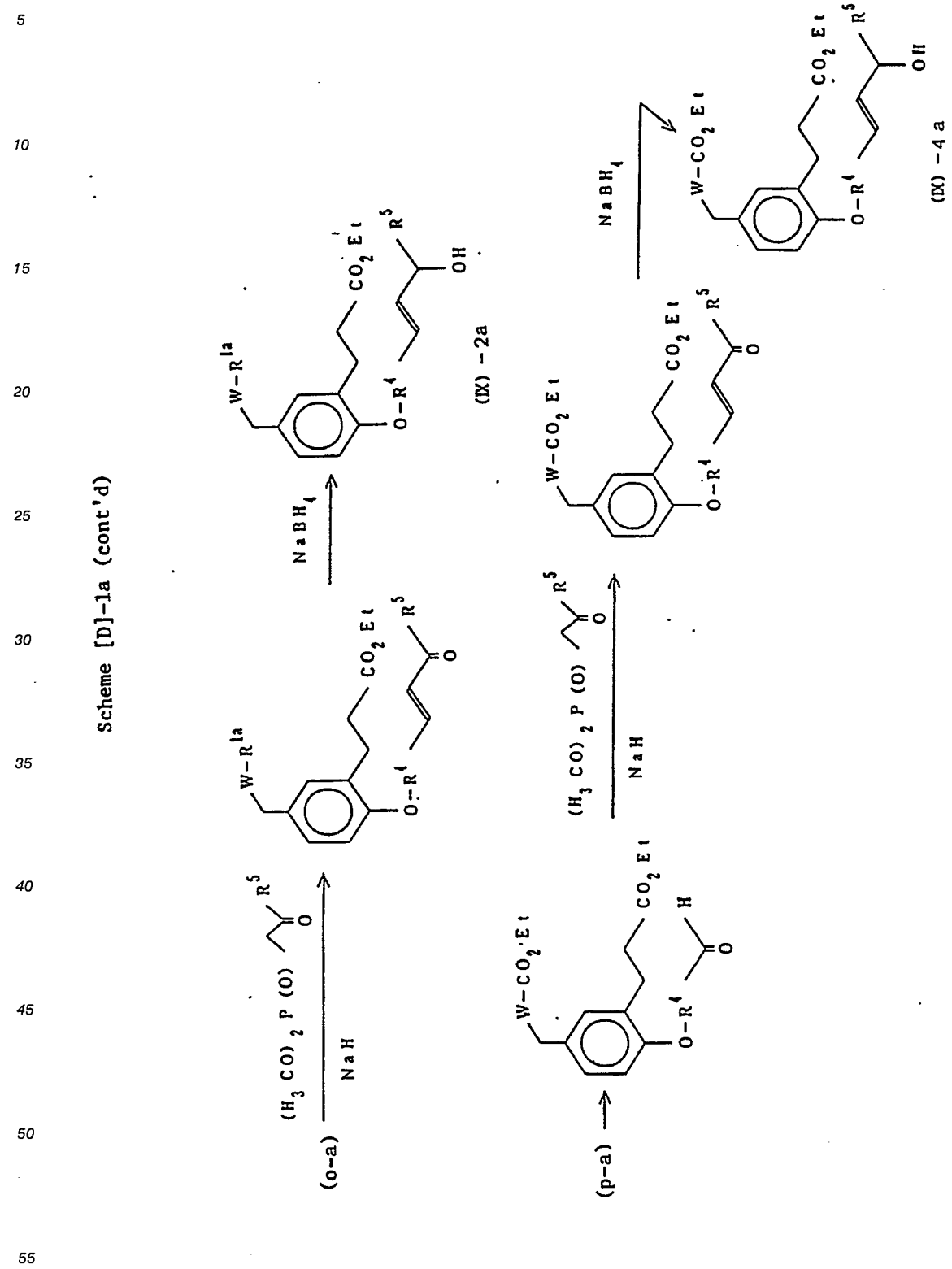
Scheme [D]-1a


cont'd on Scheme [E]-1a
NaBH4
cont'd on (o-a)
cont'd on (n-a)
D-Φa
I) DMSO, Δ
II) H2/Pd-C
III) Py•HCℓ, 200°C
SO3Py, DMSO, Et3N
H2SO4 EtOH
p-TsOH EtOH
CH2N2
NaH
Br-Z1-B1 or MsO-Z2-B2
(IX) - 1a

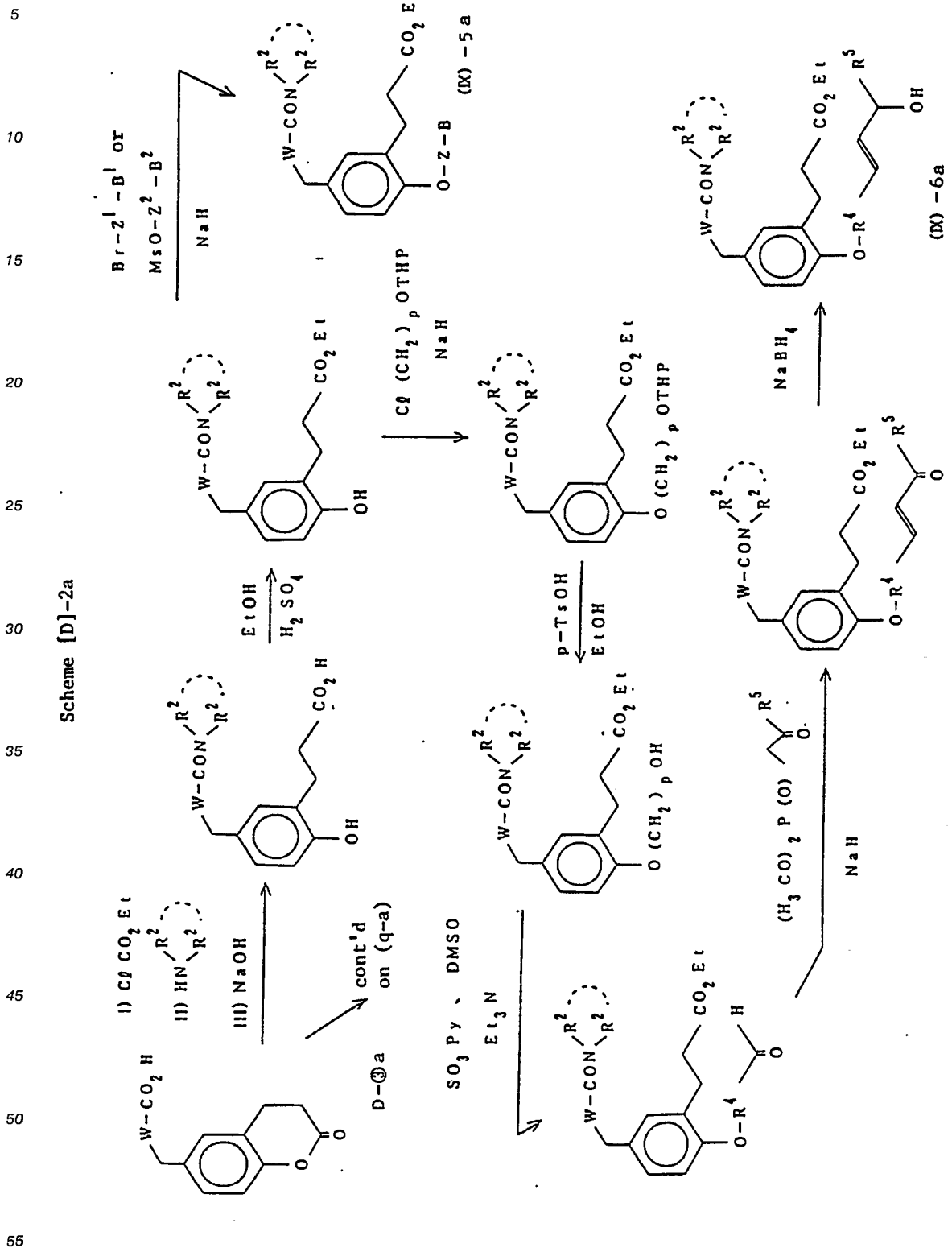
Scheme [D]-1a (cont'd)



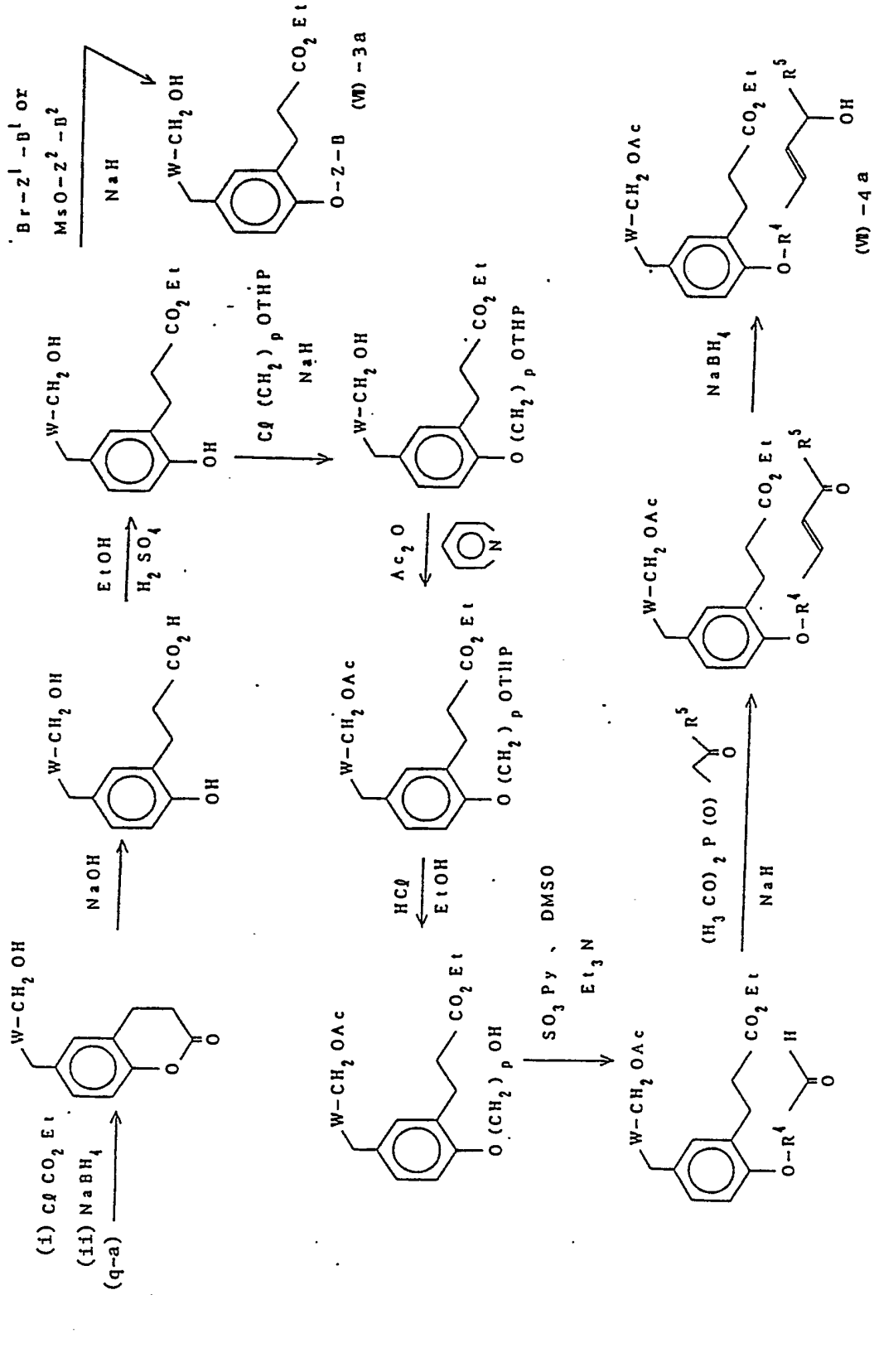
Scheme [D]-1a (cont'd)



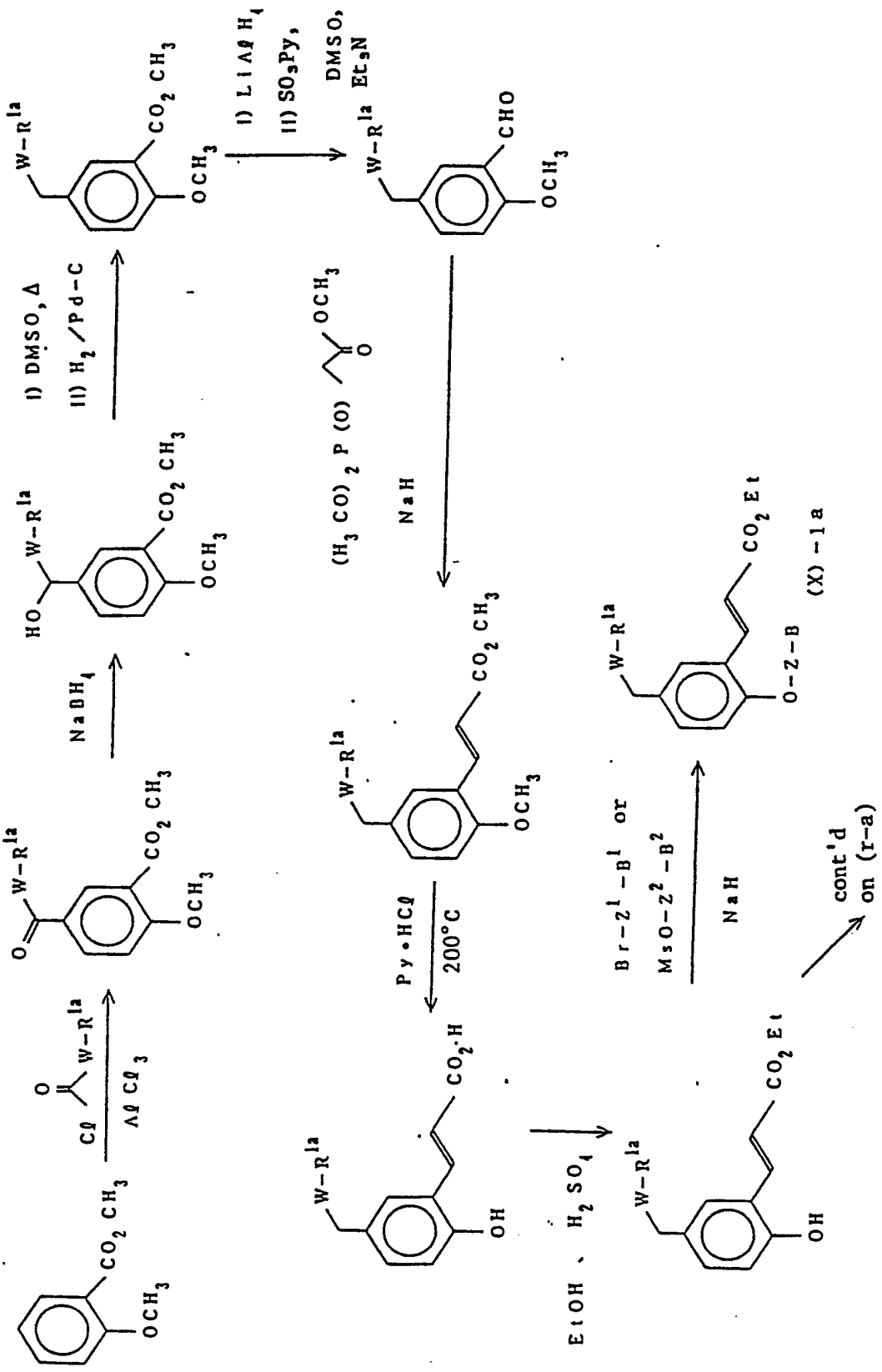
Scheme [D]-2a


Br-Z1-B1 or
MsO-Z2-B2
NaH
(IX) -5a
Cℓ (CH2)p OTHP
NaH
EtOH
H2SO4
p-TsOH
EtOH
NaBH4
(H3CO)2P(O)
NaH
SO3 Py , DMSO
Et3N
I) Cℓ CO2Et
II) HN
III) NaOH
cont'd
on (q-a)
D-③a
(IX) -6a

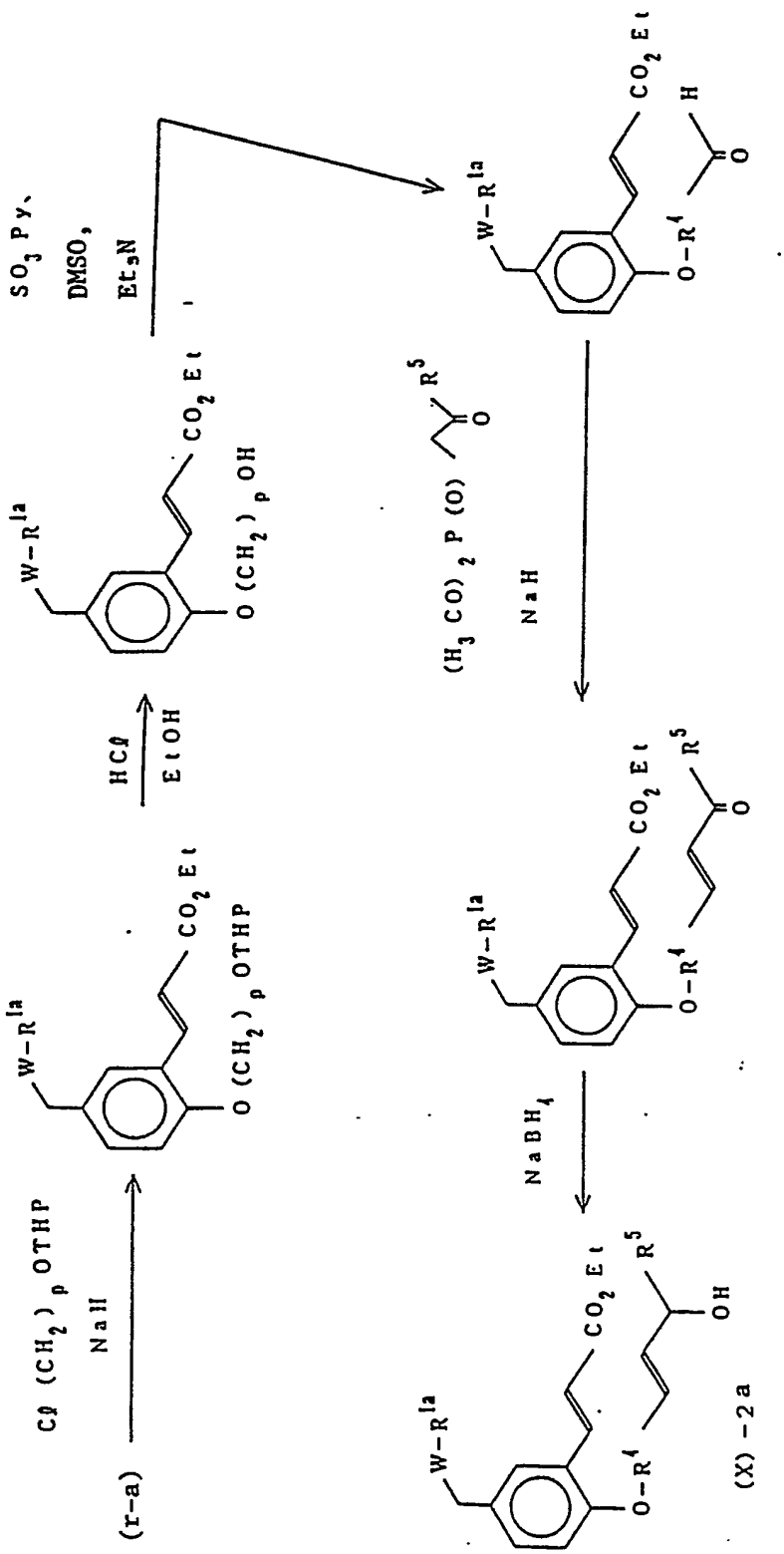
Scheme [D]-2a (cont'd)



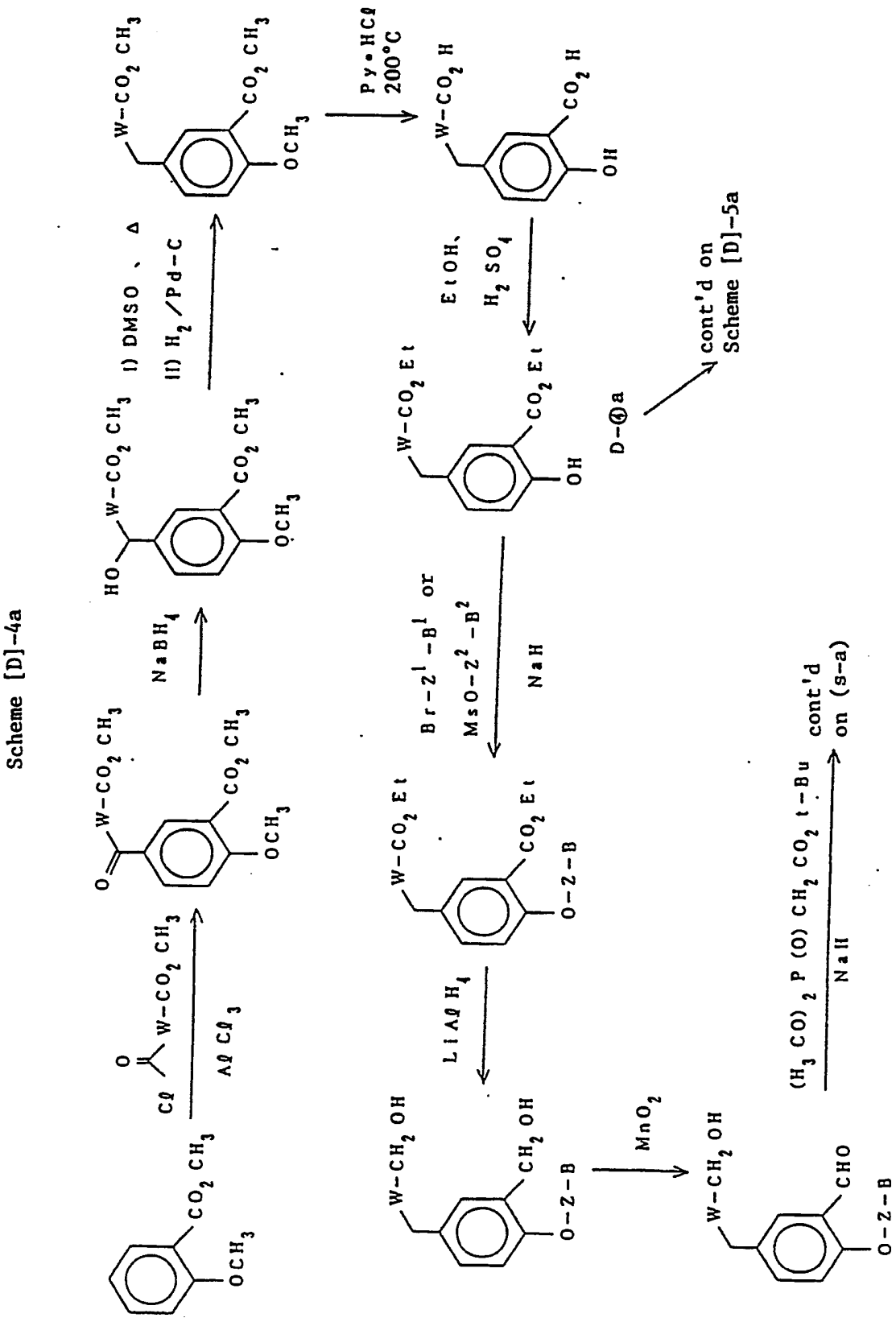
Scheme [D]-3a


W-R1a
CO2CH3
OCH3
1) DMSO, Δ
2) H2/Pd-C
1) LiAlH4
2) SO3Py, DMSO, Et3N
CHO
HO
NaBH4
(H3CO)2P(O)
O
OCH3
NaH
Cl
AlCl3
Py·HCl
200°C
CO2H
OH
EtOH, H2SO4
CO2Et
Br-Z1-B1 or
MsO-Z2-B2
O-Z-B
(X)-1a
cont'd
on (r-a)

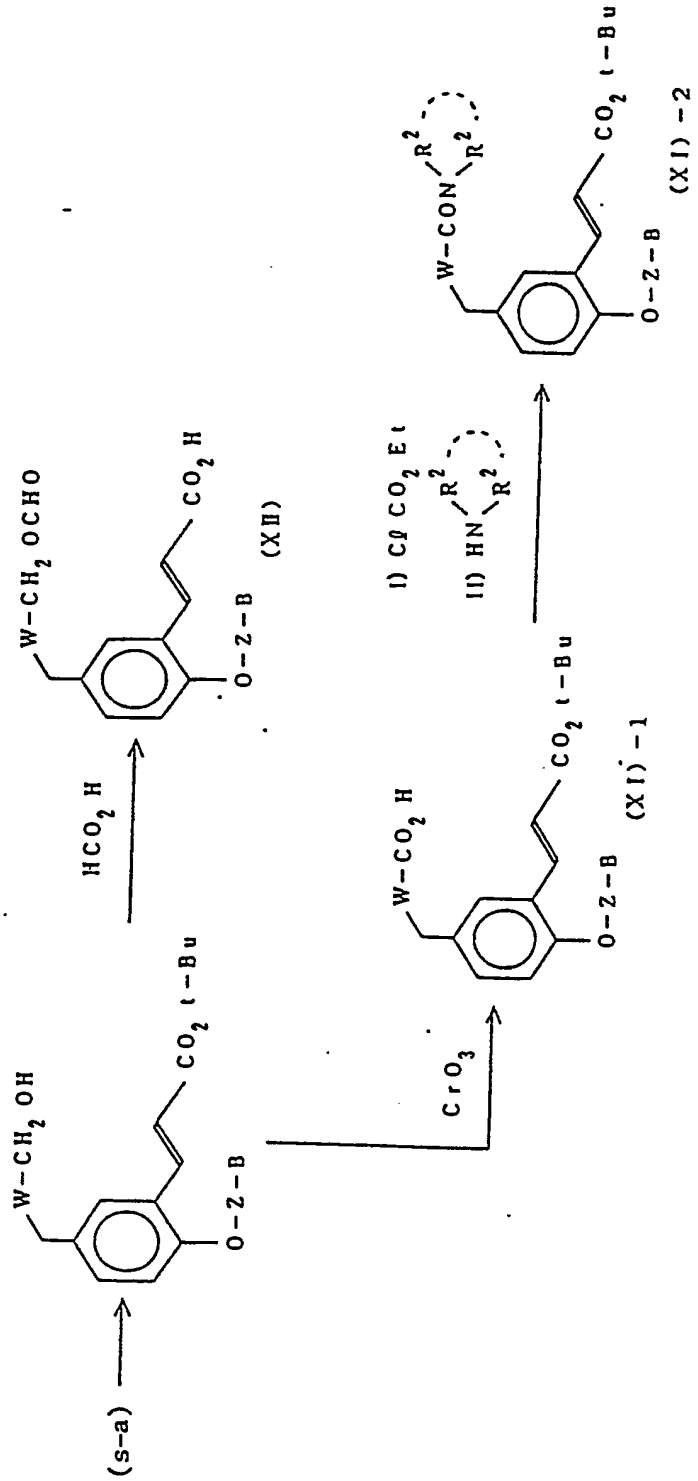
Scheme [D]-3a (cont'd)



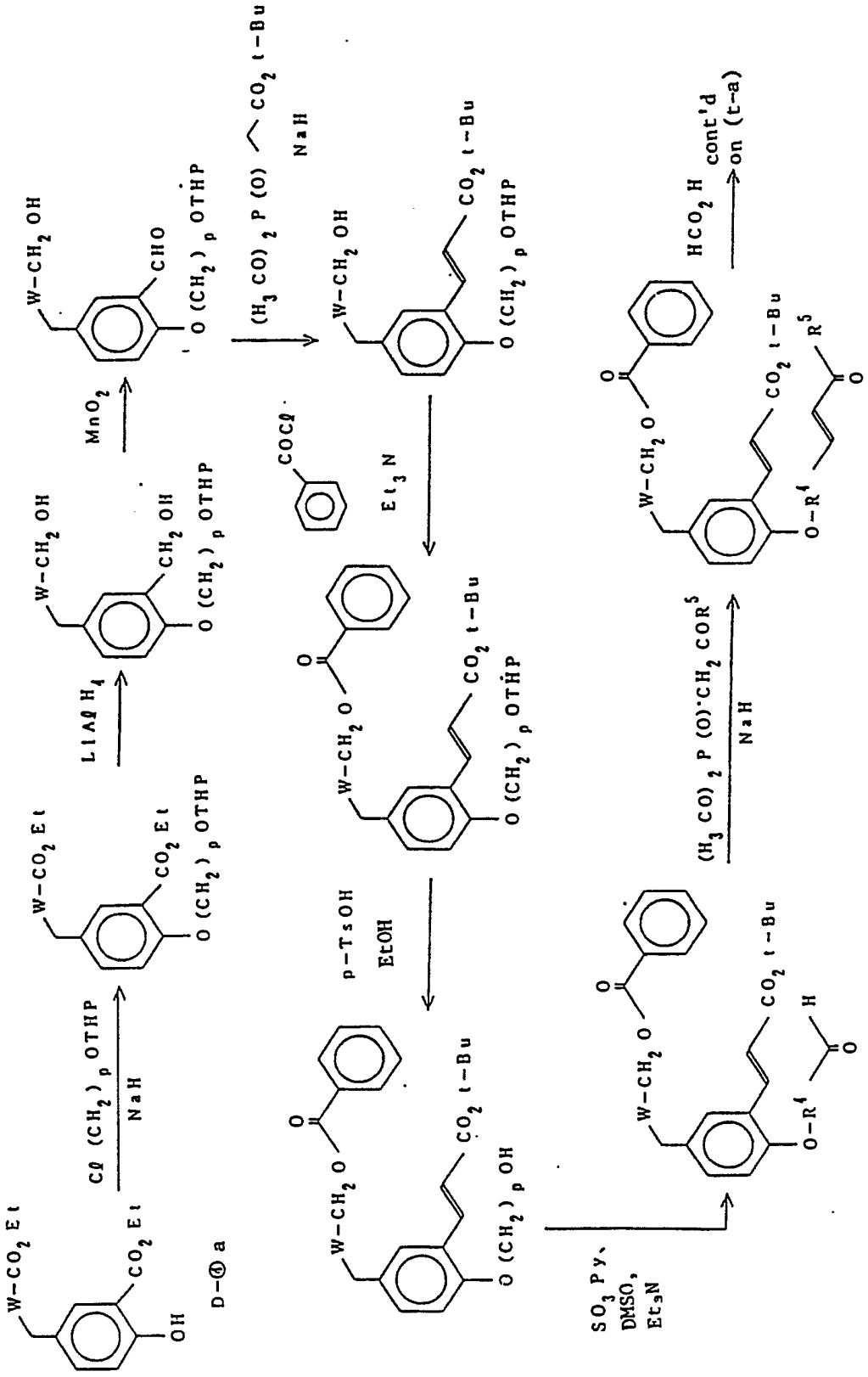
Scheme [D]-4a


W-CO2CH3
CO2CH3
OCH3
Cl
O
AlCl3
NaBH4
HO
1) DMSO, Δ
II) H2/Pd-C
Py·HCl
200°C
OH
EtOH,
H2SO4
CO2Et
D-④a
cont'd on
Scheme [D]-5a
Br-Z1-B1 or
MsO-Z2-B2
NaH
O-Z-B
LiAlH4
CH2OH
MnO2
CHO
(H3CO)2P(O)CH2CO2t-Bu
NaH
cont'd
on (s-a)

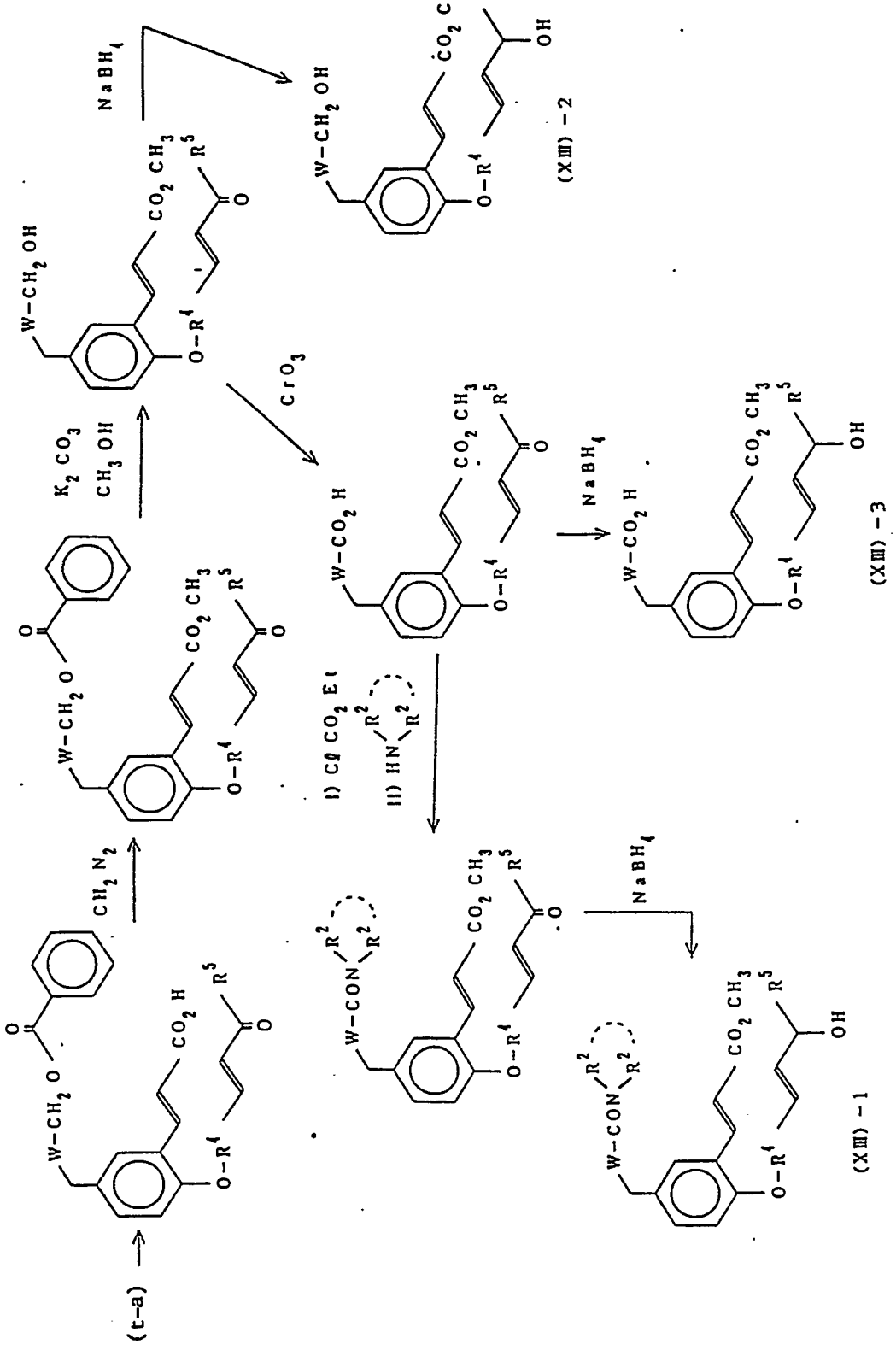
Scheme [D]-4a (cont'd)



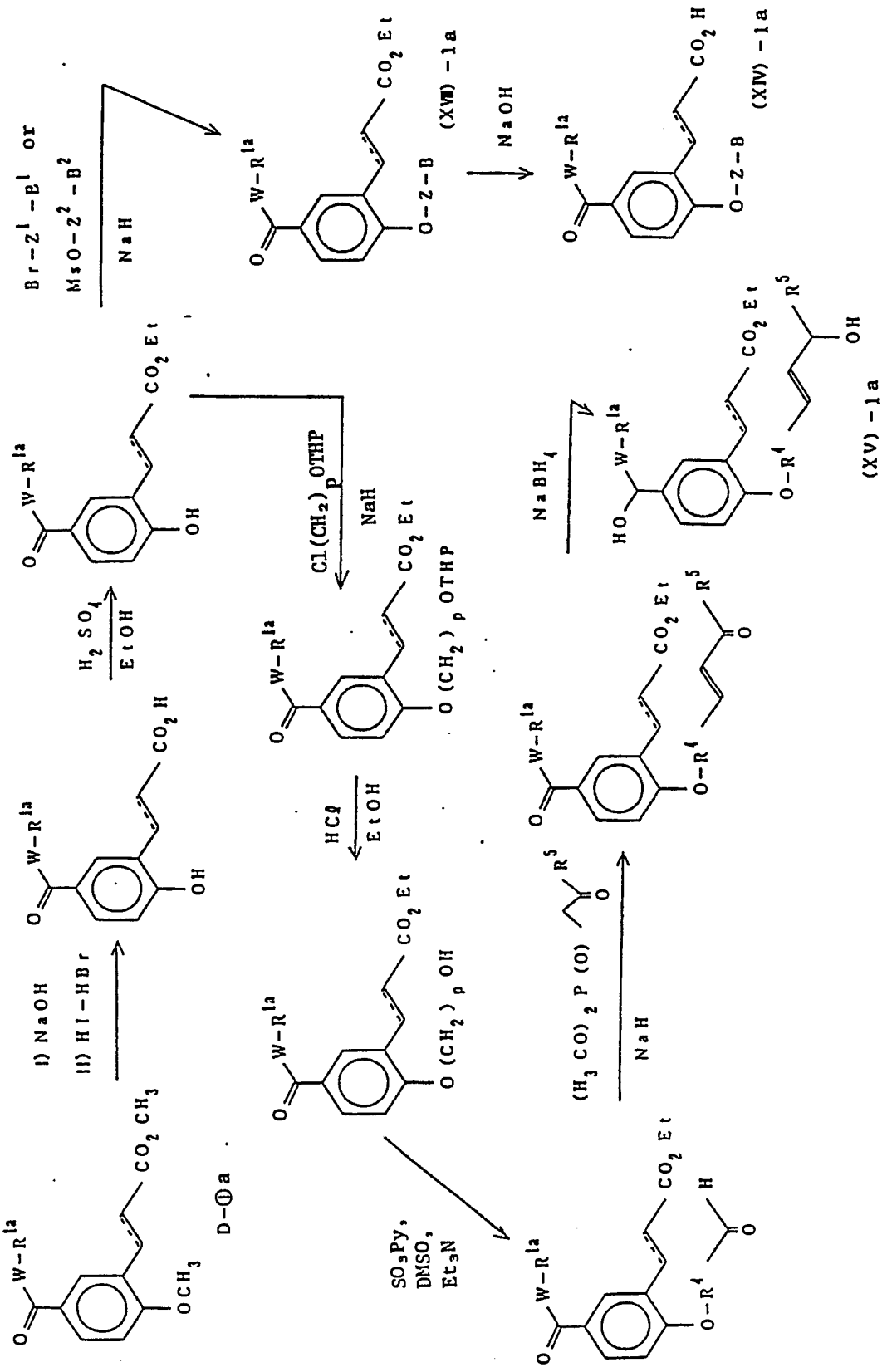
Scheme [D]-5a


W-CO2Et
CO2Et
OH
D-① a
Cℓ(CH2)pOTHP
NaH
W-CO2Et
CO2Et
O(CH2)pOTHP
LiAℓH4
W-CH2OH
CH2OH
O(CH2)pOTHP
MnO2
W-CH2OH
CHO
O(CH2)pOTHP
(H3CO)2P(O)CH2CO2t-Bu
NaH
W-CH2OH
CO2t-Bu
O(CH2)pOTHP
COCℓ
Et3N
W-CH2O
O
CO2t-Bu
O(CH2)pOTHP
p-TsOH
EtOH
W-CH2O
O
CO2t-Bu
O(CH2)pOH
SO3Py,
DMSO,
Et3N
(H3CO)2P(O)·CH2COR5
NaH
HCO2H
cont'd
on (t-a)

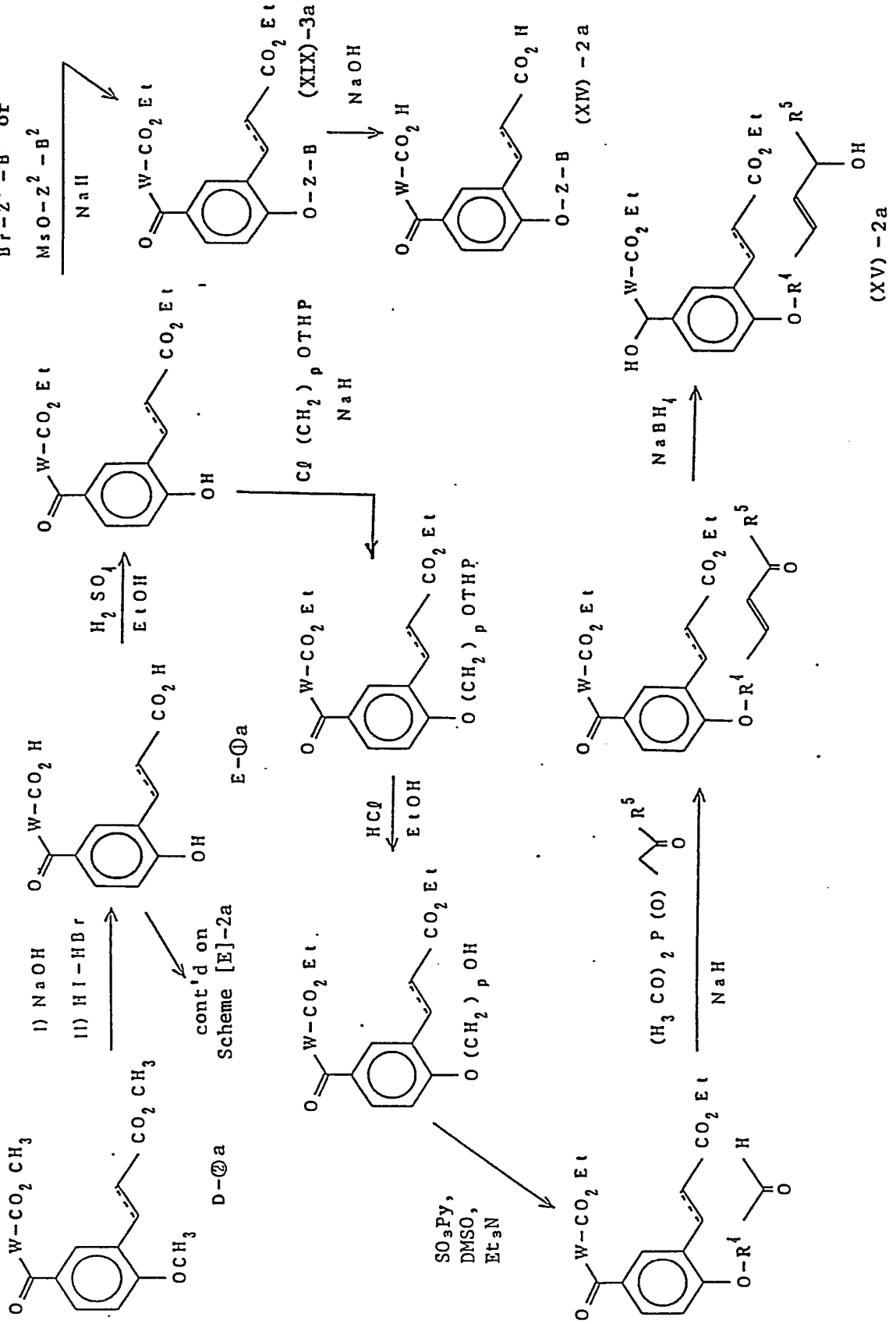
Scheme [D]-5a (cont'd)



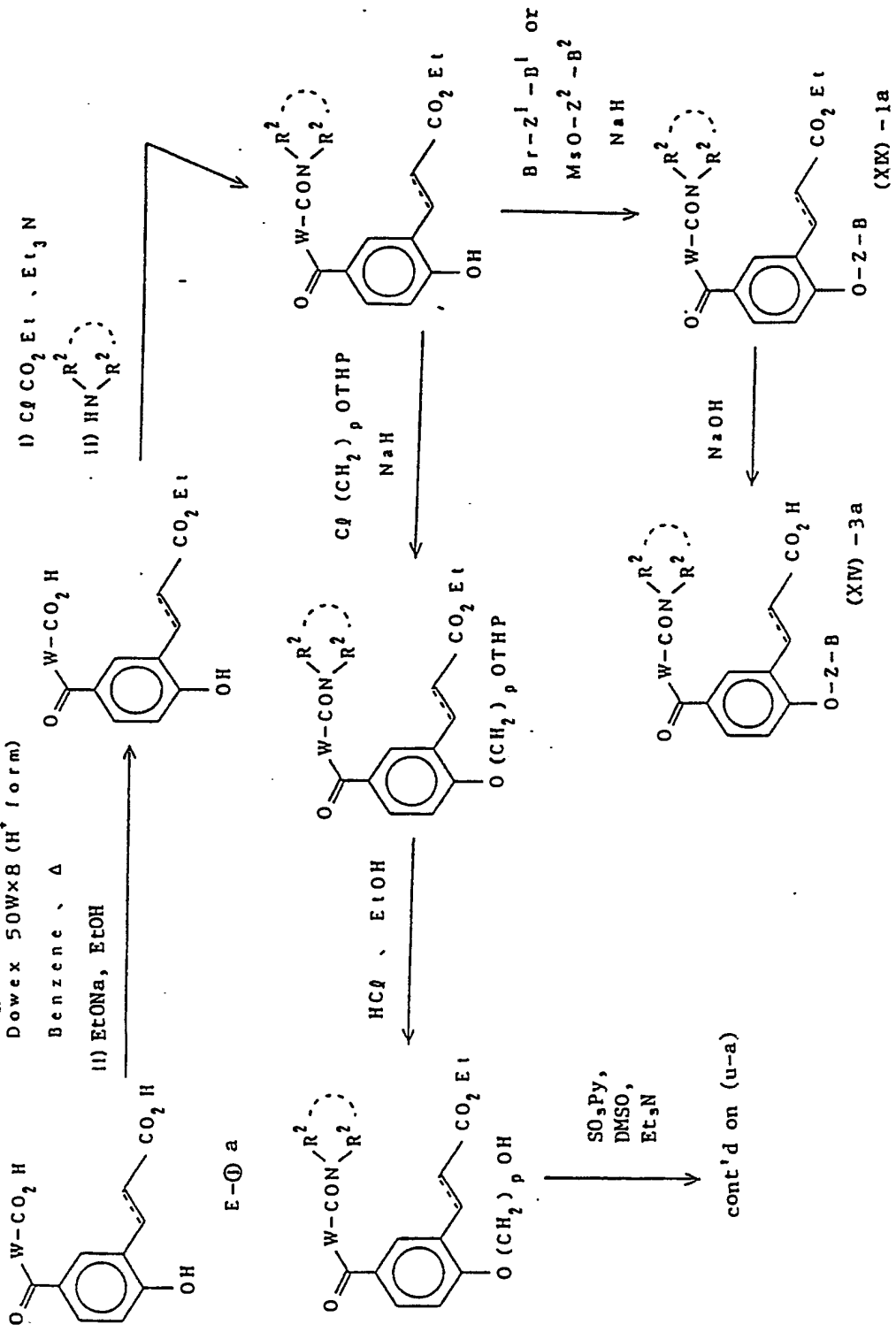
Scheme [E]-1a


Br-Z1-B1 or
MsO-Z2-B2
NaH
(XVII)-1a
NaOH
(XIV)-1a
H2SO4
EtOH
Cl(CH2)pOTHP
NaH
NaBH4
(XV)-1a
HCl
EtOH
(H3CO)2P(O)
NaH
1) NaOH
2) HI-HBr
D-①a
SO3Py,
DMSO,
Et3N

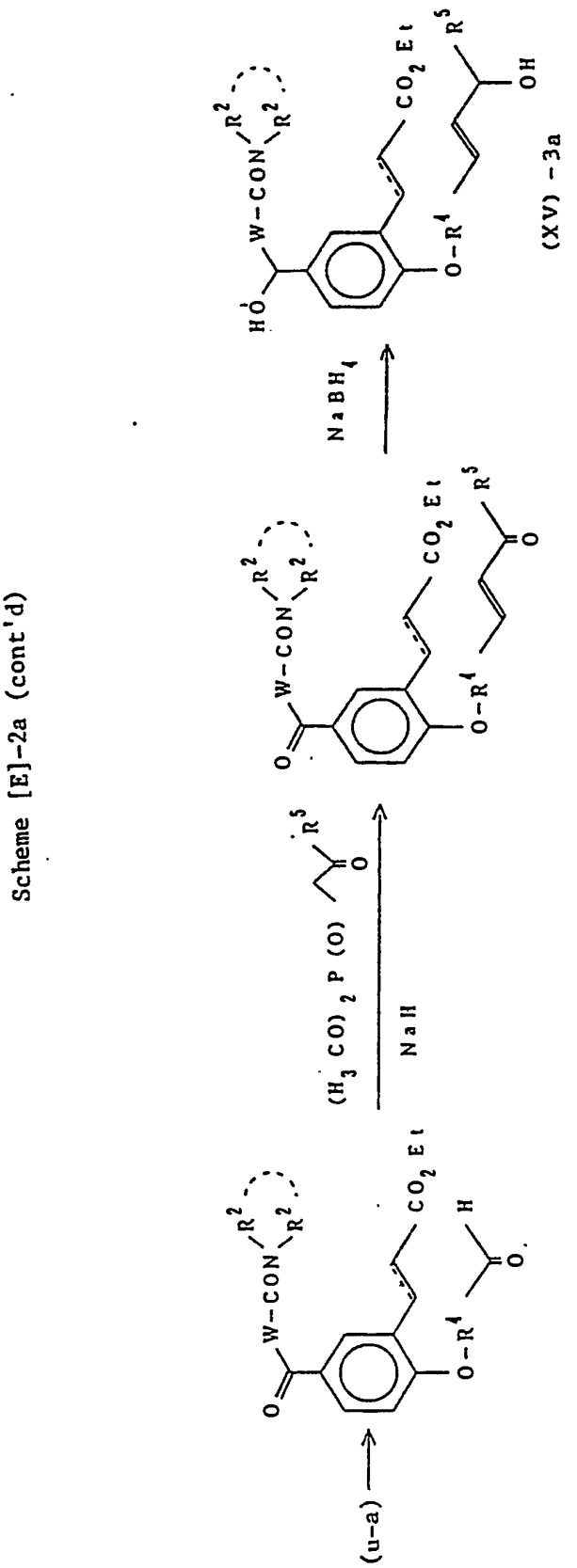
Scheme [E]-1a (cont'd)



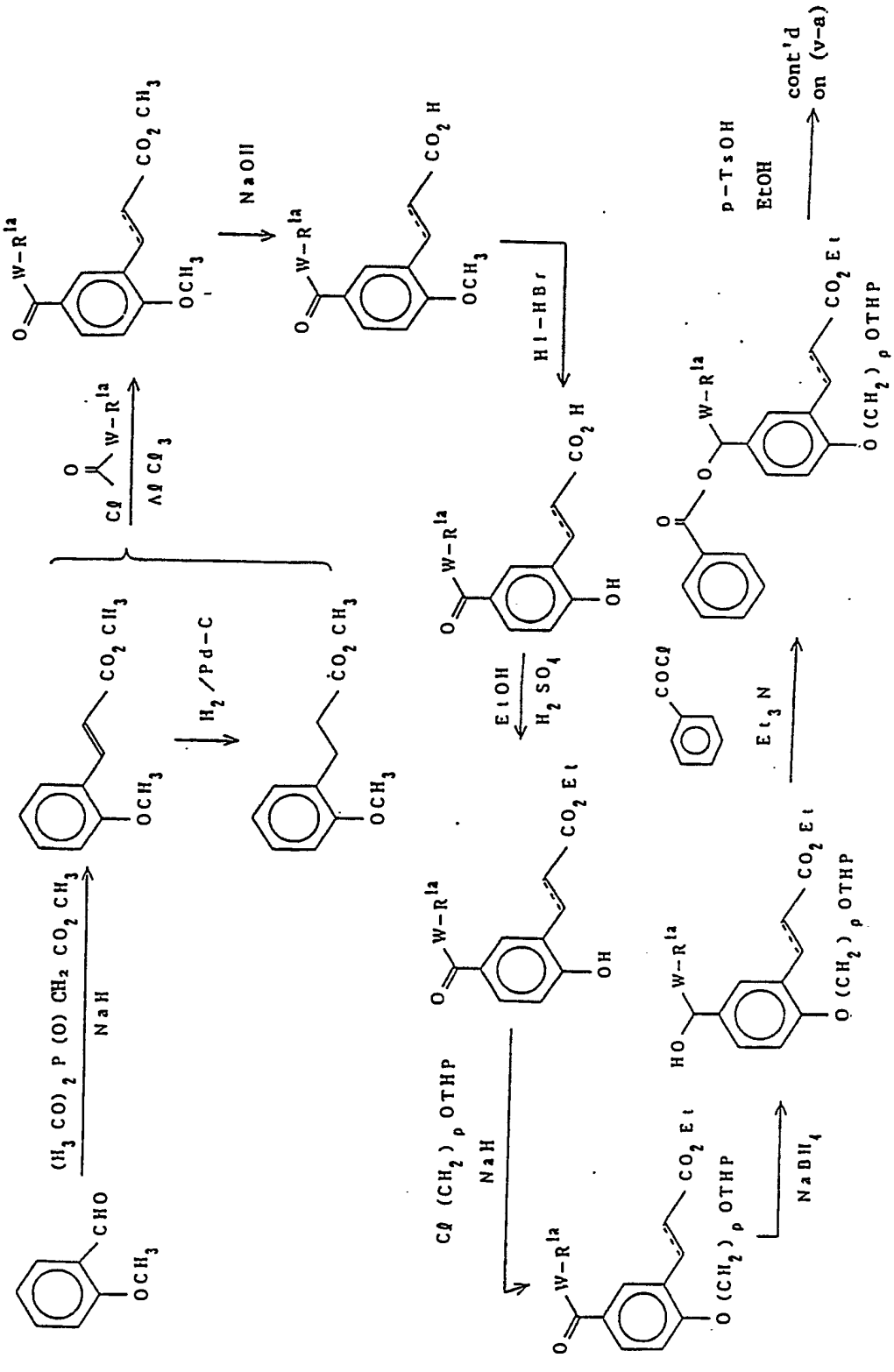
Scheme [E]-2a


i) •HCl, 200°C or
Dowex 50W×8 (H⁺ form)
Benzene, Δ
ii) EtONa, EtOH
E-① a
i) ClCO2Et, Et3N
ii) HN(R2)(R2)
Cl(CH2)pOTHP
NaH
HCl, EtOH
SO3Py, DMSO, Et3N
cont'd on (u-a)
Br-Z1-B1 or MsO-Z2-B2
NaH
NaOH
(XIV) -3a
(XX) -1a

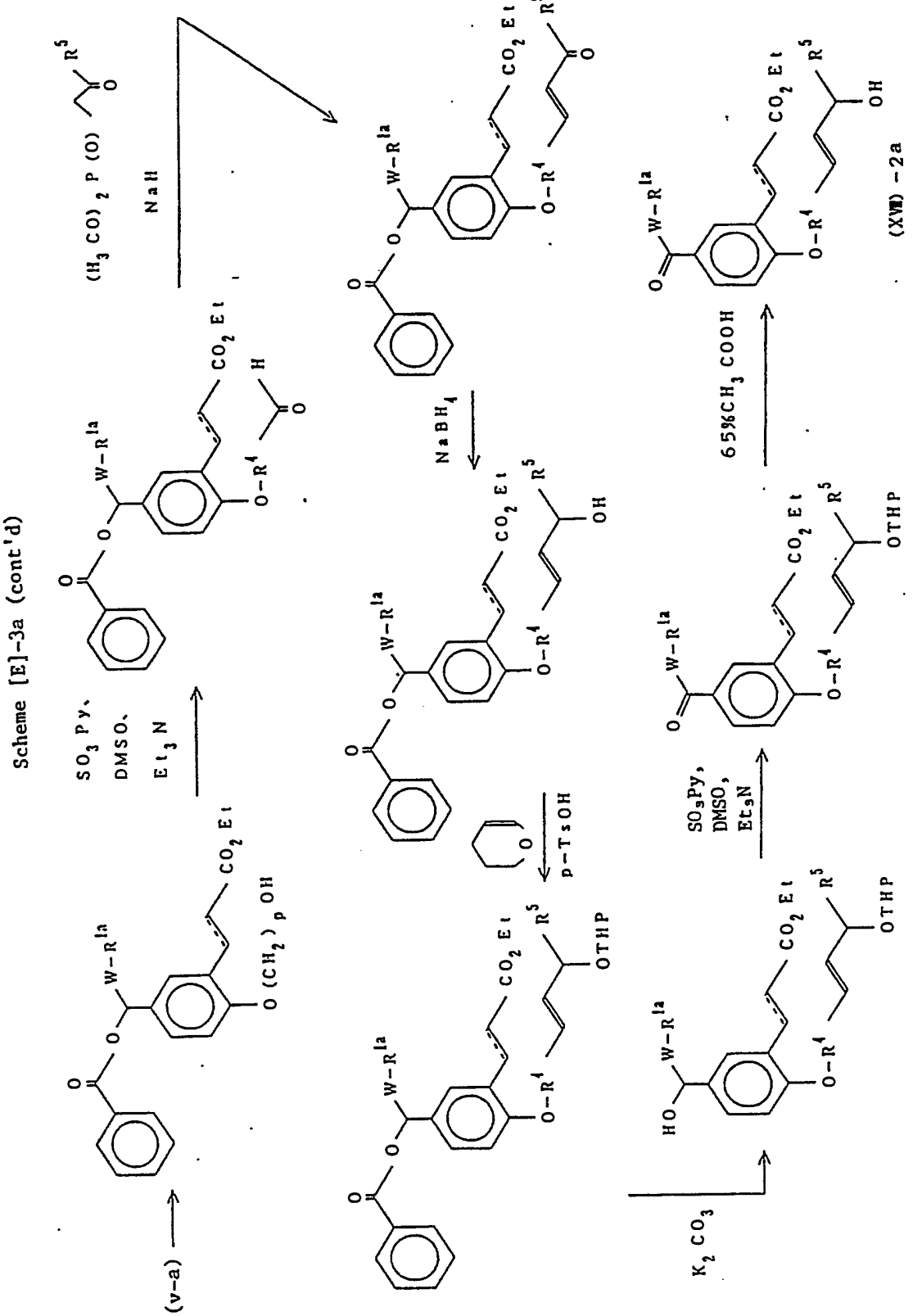
Scheme [E]-2a (cont'd)



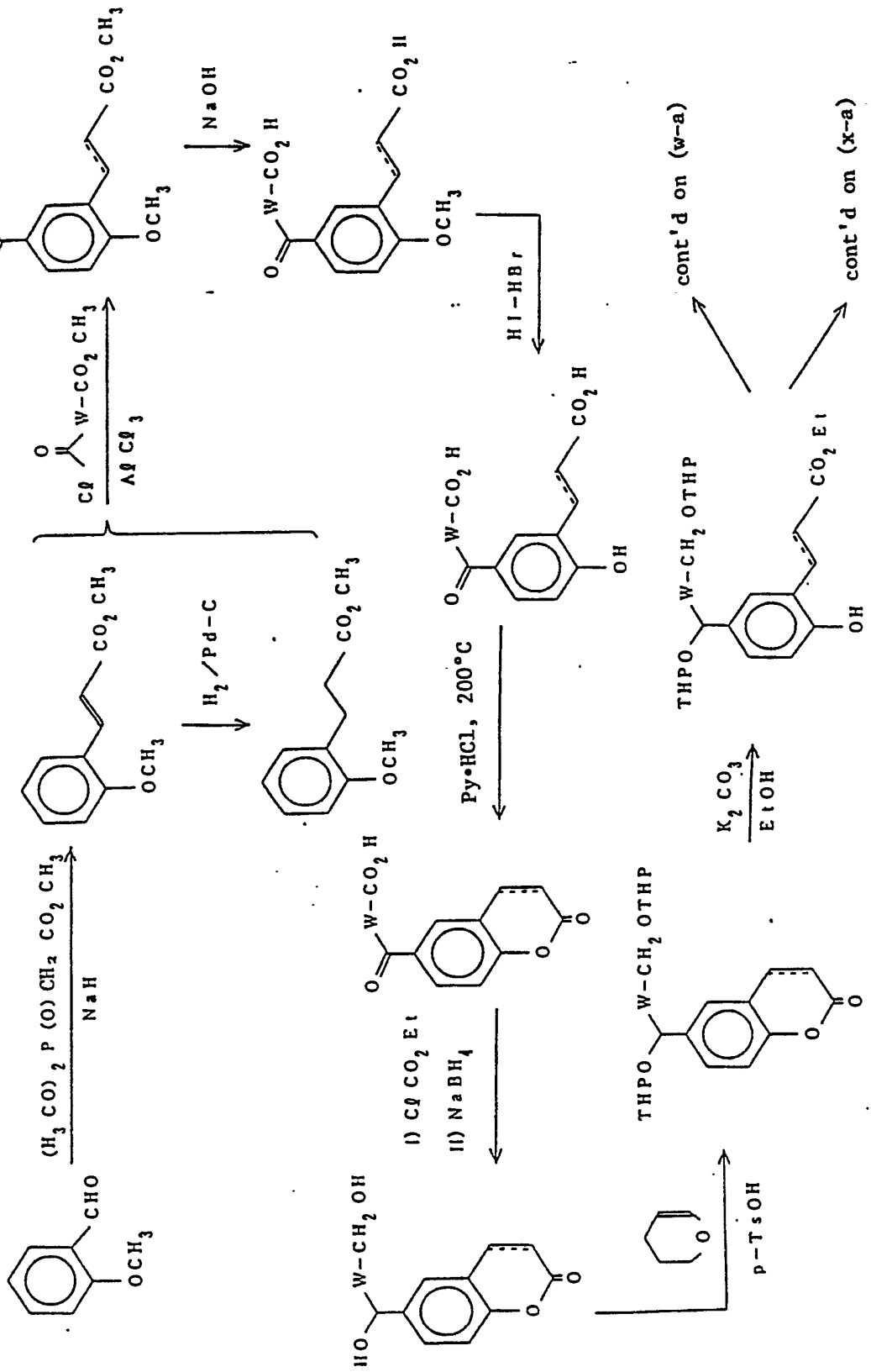
Scheme [E]-3a


(H3CO)2P(O)CH2CO2CH3
NaH
CHO
OCH3
CO2CH3
H2/Pd-C
ClCO(CH2)pOTHP
AlCl3
NaOH
CO2H
HI-HBr
EtOH
H2SO4
COCl
Et3N
p-TsOH
EtOH
CO2Et
O(CH2)pOTHP
NaBH4
OH
HO
W-R1a
cont'd
on (v-a)

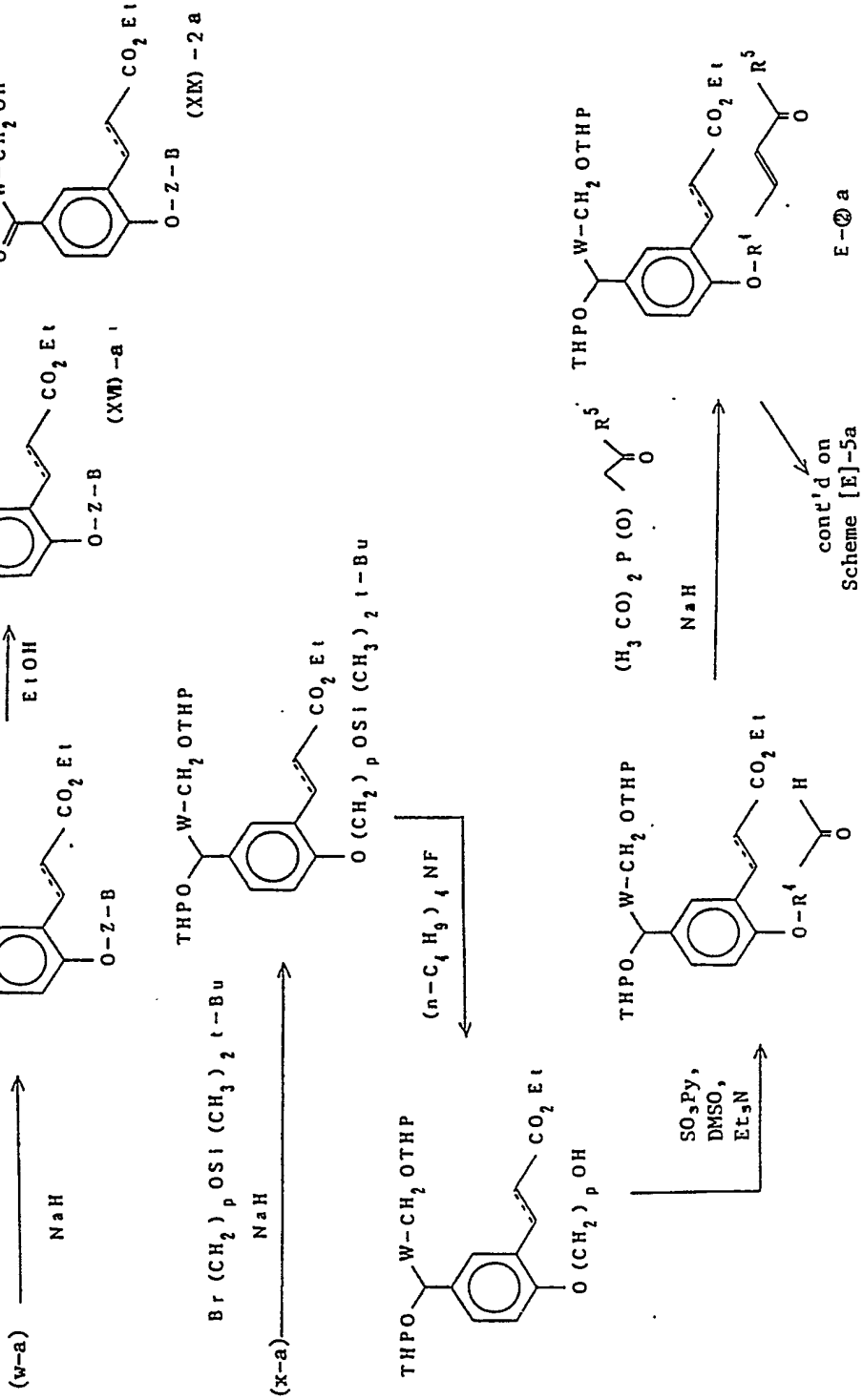
Scheme [E]-3a (cont'd)



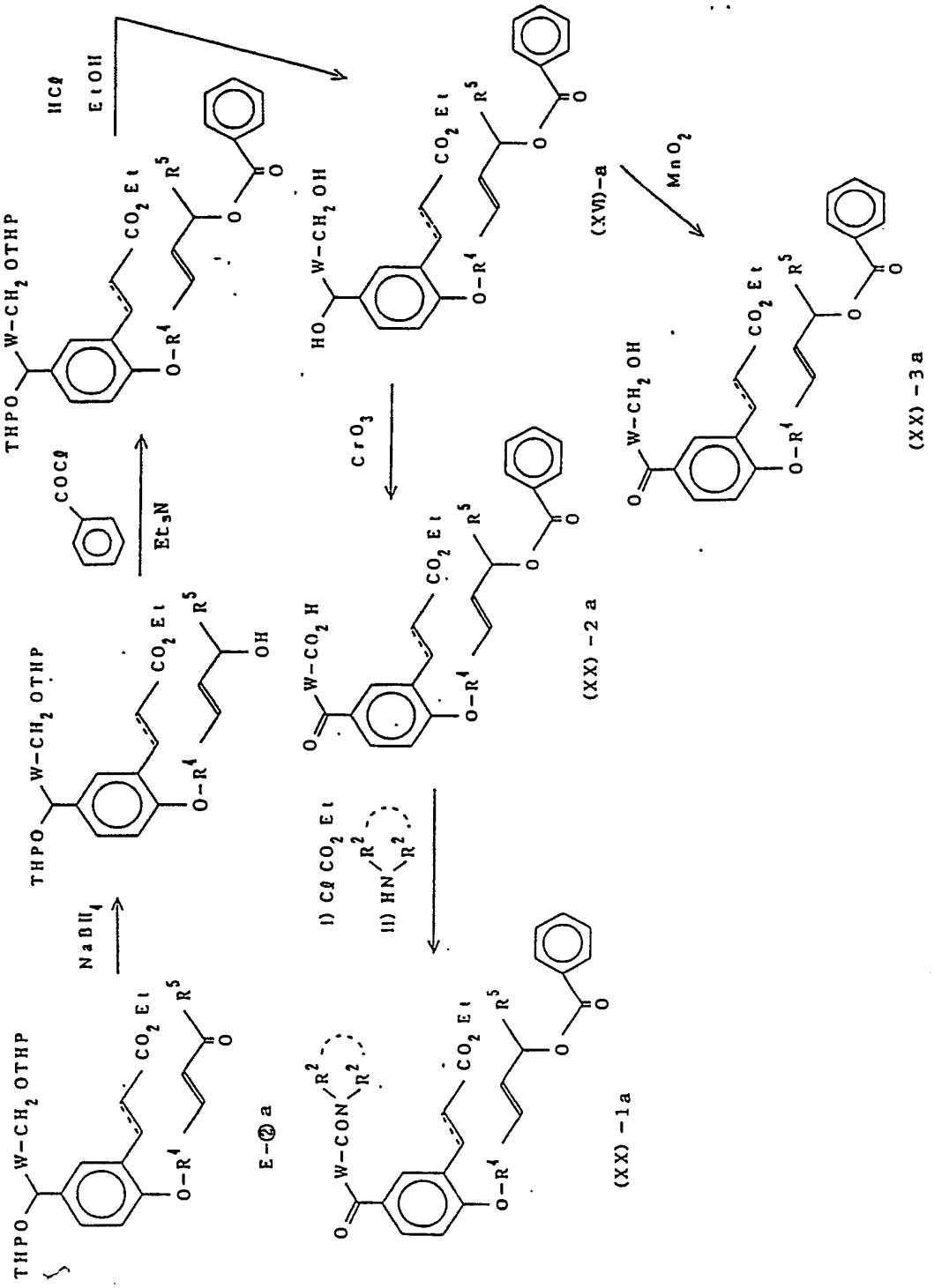
Scheme [E]-4a


CHO
OCH3
(H3CO)2P(O)CH2CO2CH3
NaH
CO2CH3
OCH3
H2/Pd-C
CO2CH3
OCH3
W-CO2CH3
OCH3
Cl
AlCl3
NaOH
W-CO2H
OCH3
HI-HBr
W-CO2H
OH
CO2H
Py•HCl, 200°C
W-CO2H
O
O
I) ClCO2Et
II) NaBH4
W-CH2OH
HO
O
O
p-TsOH
W-CH2OTHP
THPO
O
O
K2CO3
EtOH
W-CH2OTHP
THPO
OH
CO2Et
cont'd on (w-a)
cont'd on (x-a)

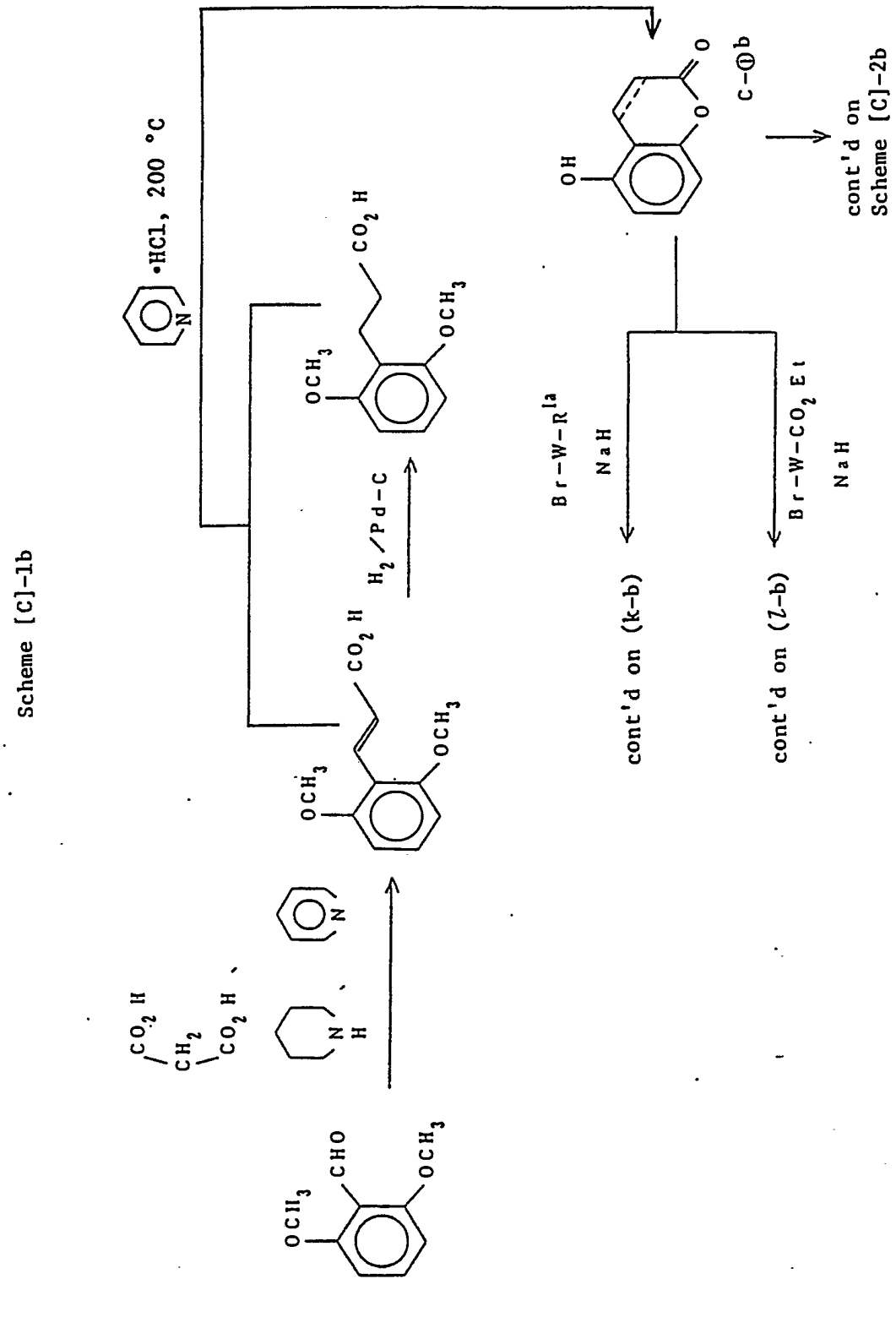
Scheme [E]-4a (cont'd)



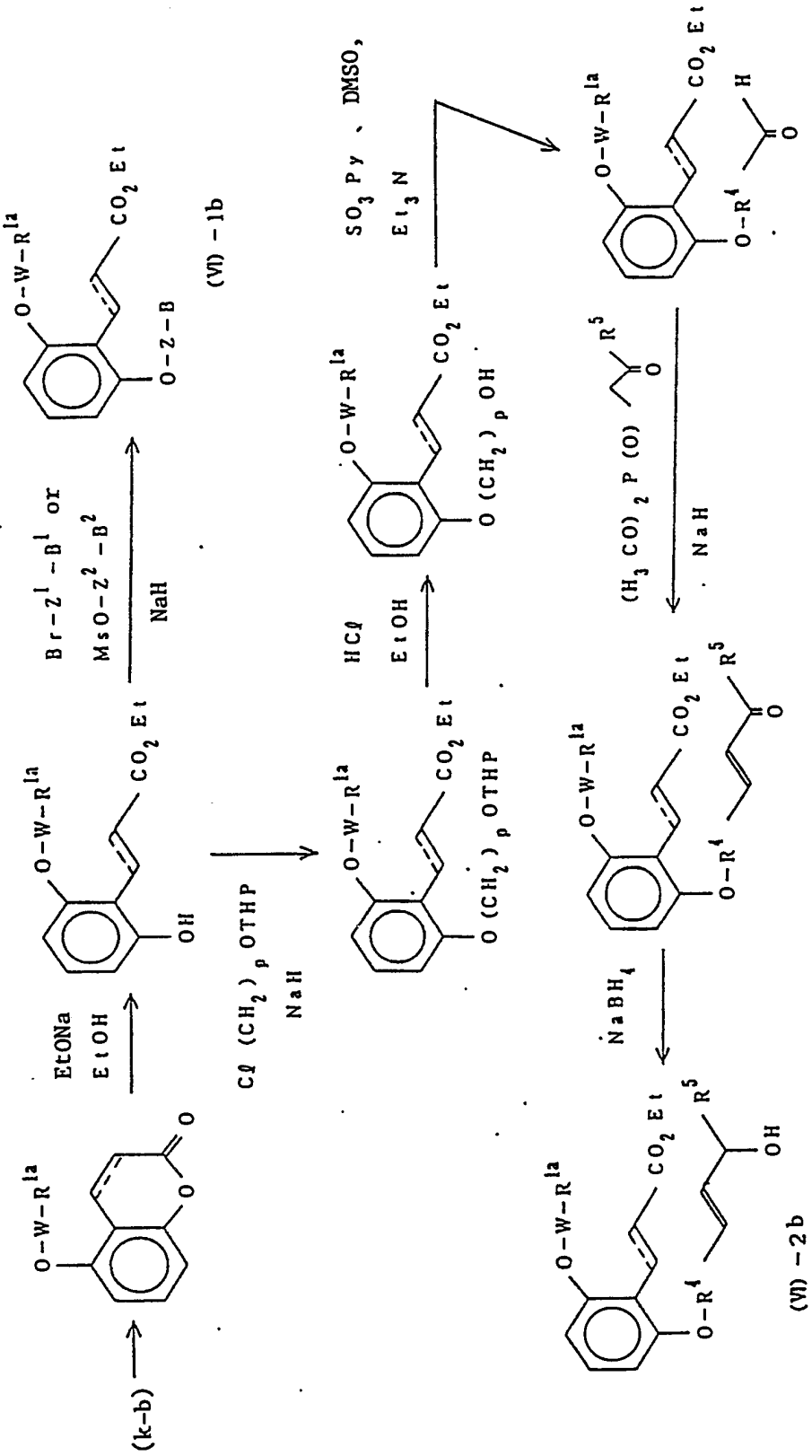
Scheme [E]-5a


HCℓ
EtOH
NaBH4
Et3N
COCℓ
CrO3
MnO2
(XVI)-a
E-②a
(XX)-1a
(XX)-2a
(XX)-3a
i) Cℓ CO2Et
ii) HN

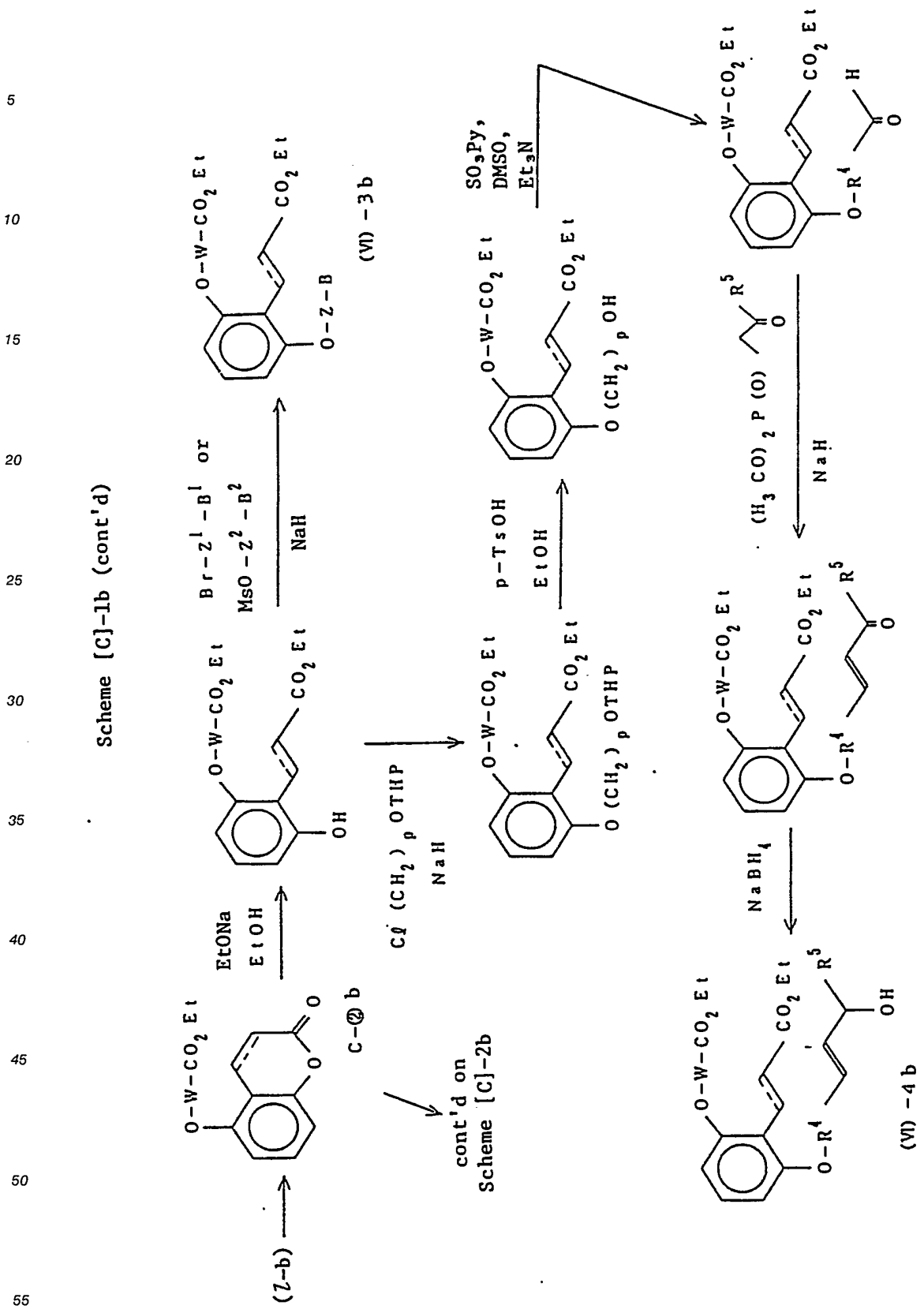
Scheme [C]-1b


•HCl, 200 °C
CO2H
CH2
CO2H
CHO
OCH3
H2/Pd-C
Br-W-R1a
NaH
Br-W-CO2Et
NaH
OH
O
C-①b
cont'd on (k-b)
cont'd on (ℓ-b)
cont'd on Scheme [C]-2b

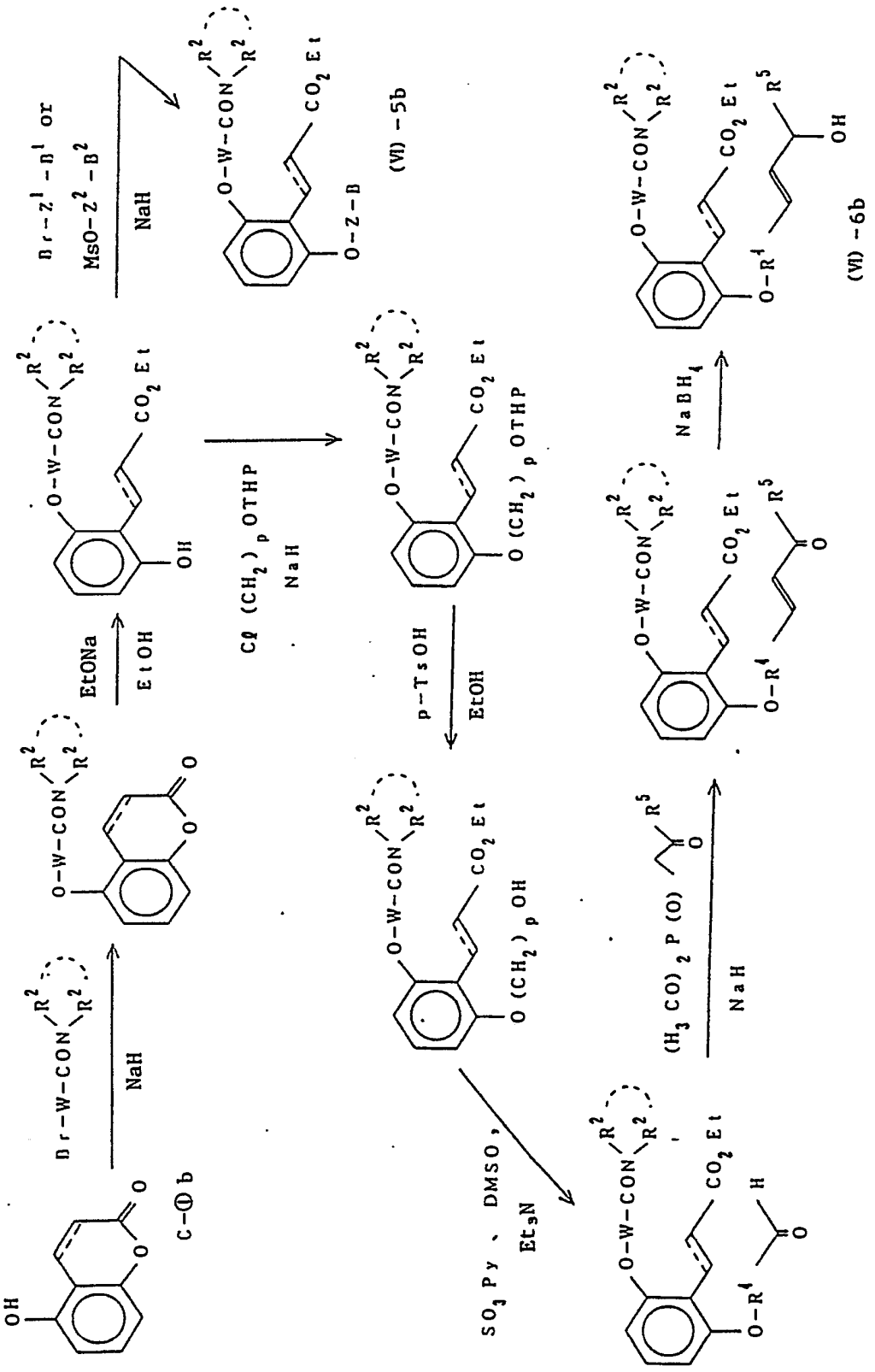
Scheme [C]-1b (cont'd)



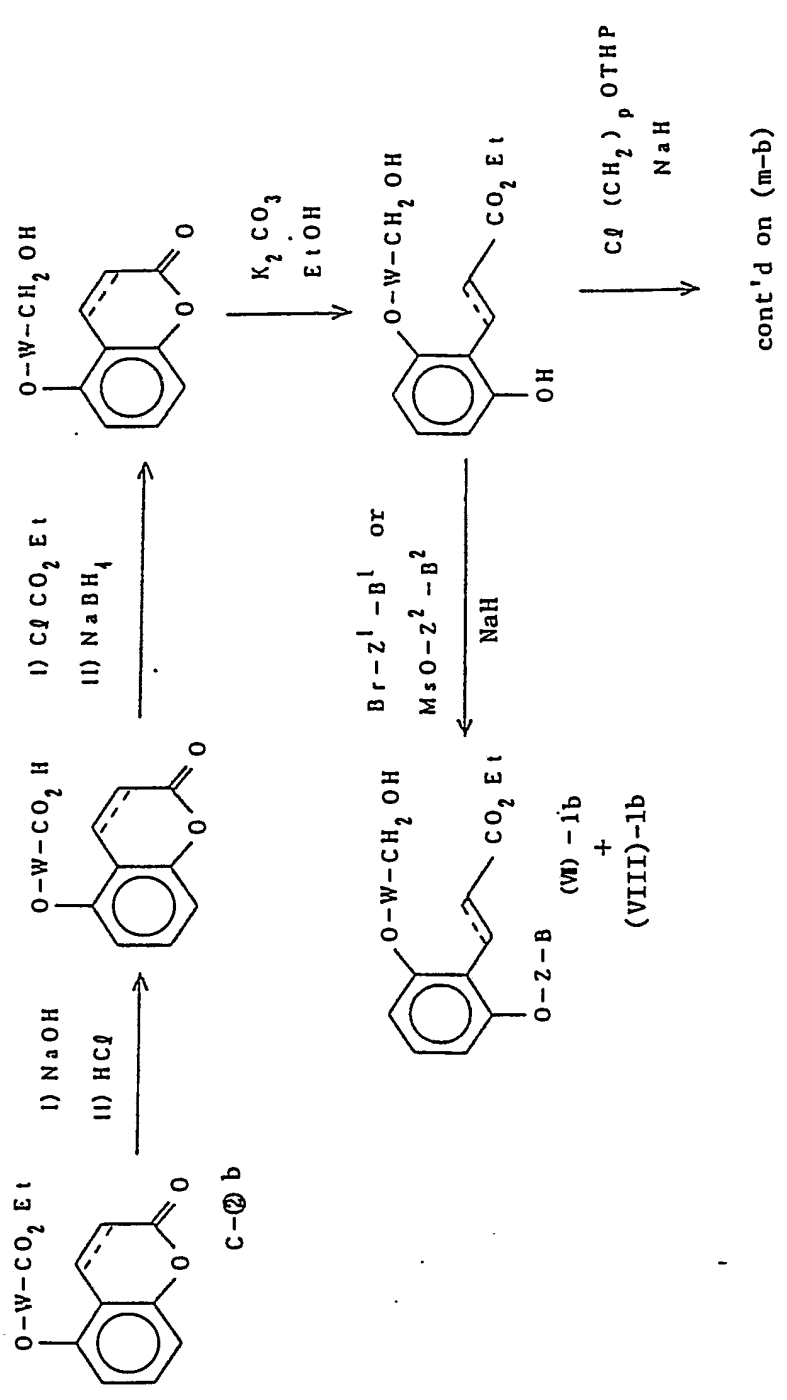
Scheme [C]-1b (cont'd)



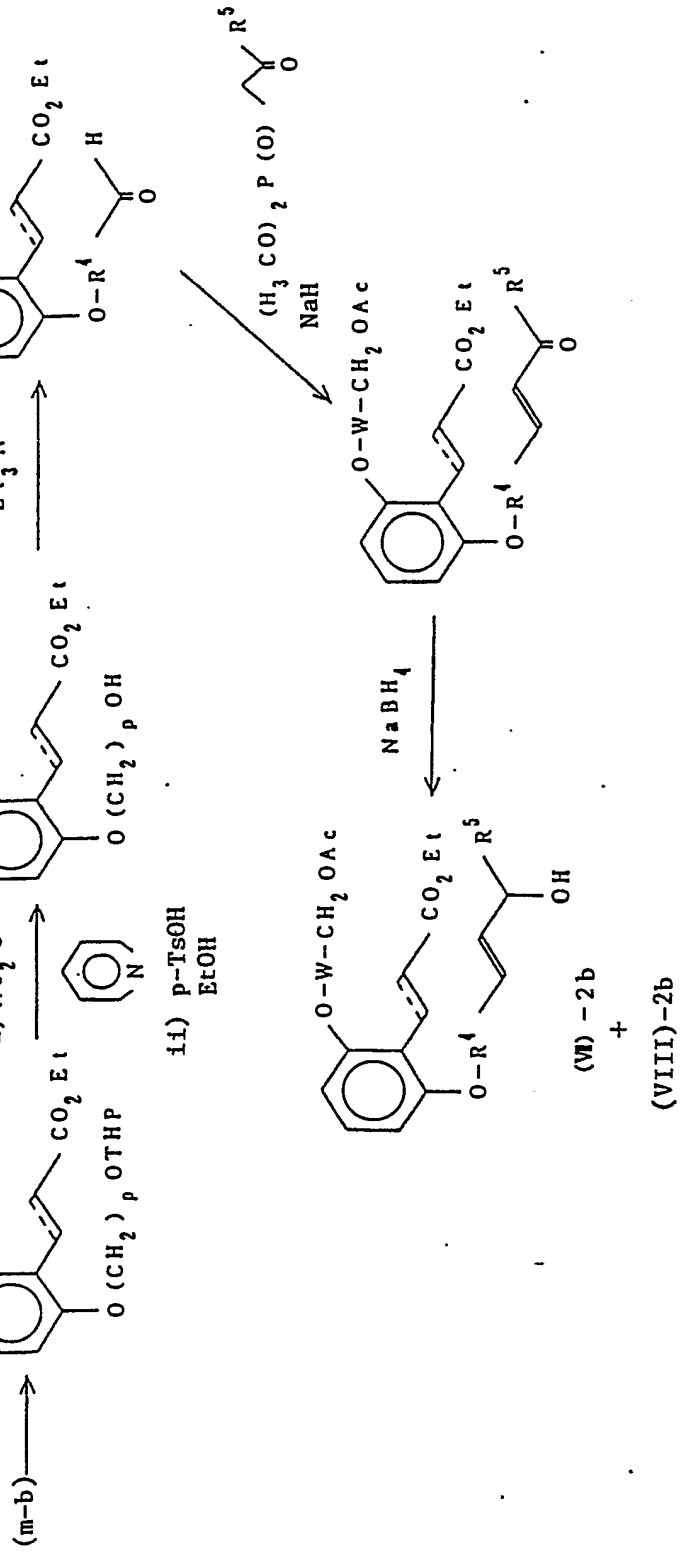
Scheme [C]-2b


Br-W-CON(R2)(R2)
NaH
C-①b
EtONa
EtOH
Cℓ(CH2)pOTHP
NaH
Br-Z1-B1 or
MsO-Z2-B2
NaH
(VI)-5b
p-TsOH
EtOH
SO3Py, DMSO,
Et3N
(H3CO)2P(O)
NaH
NaBH4
(VI)-6b

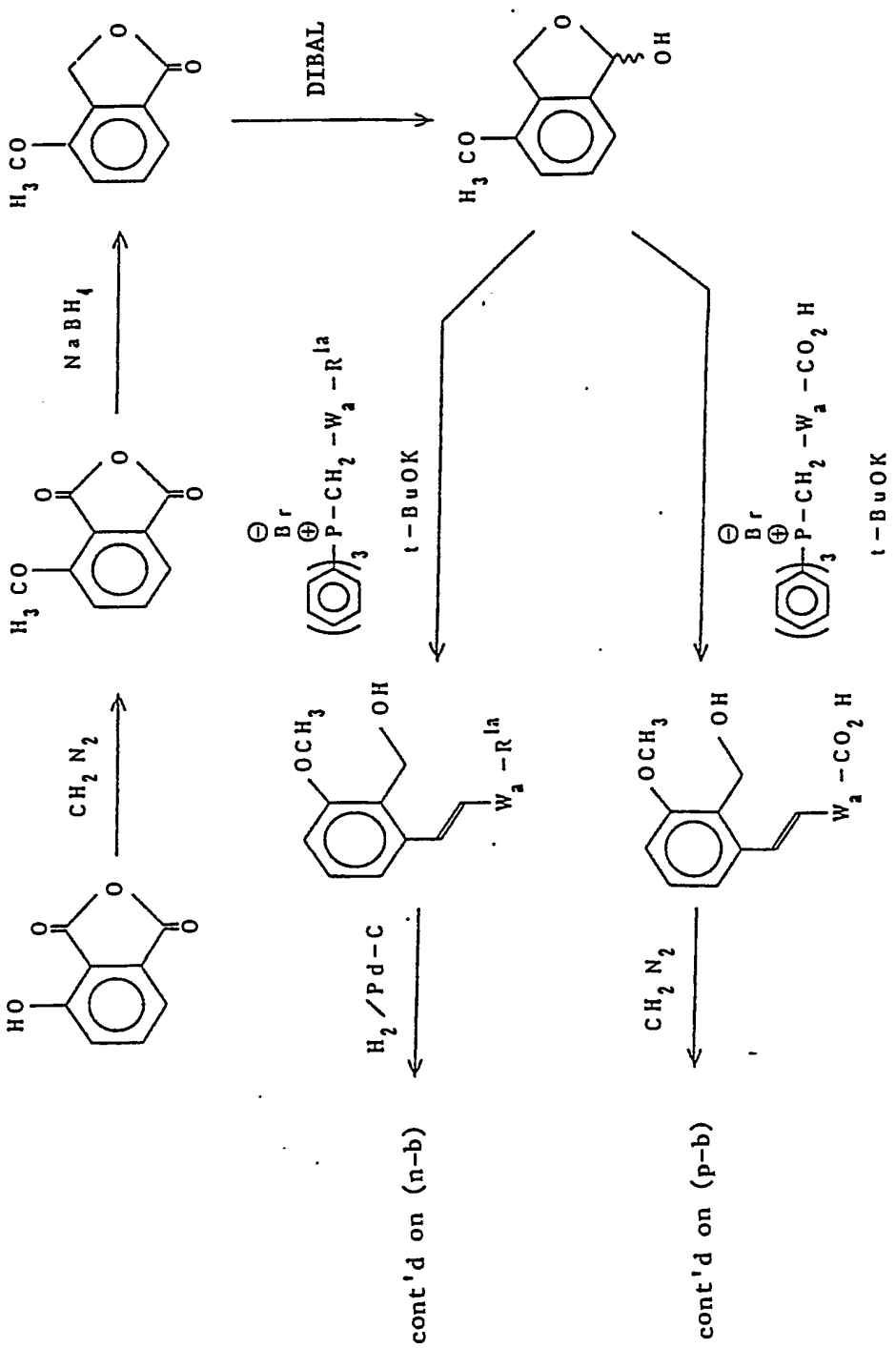
Scheme [C]-2b (cont'd)



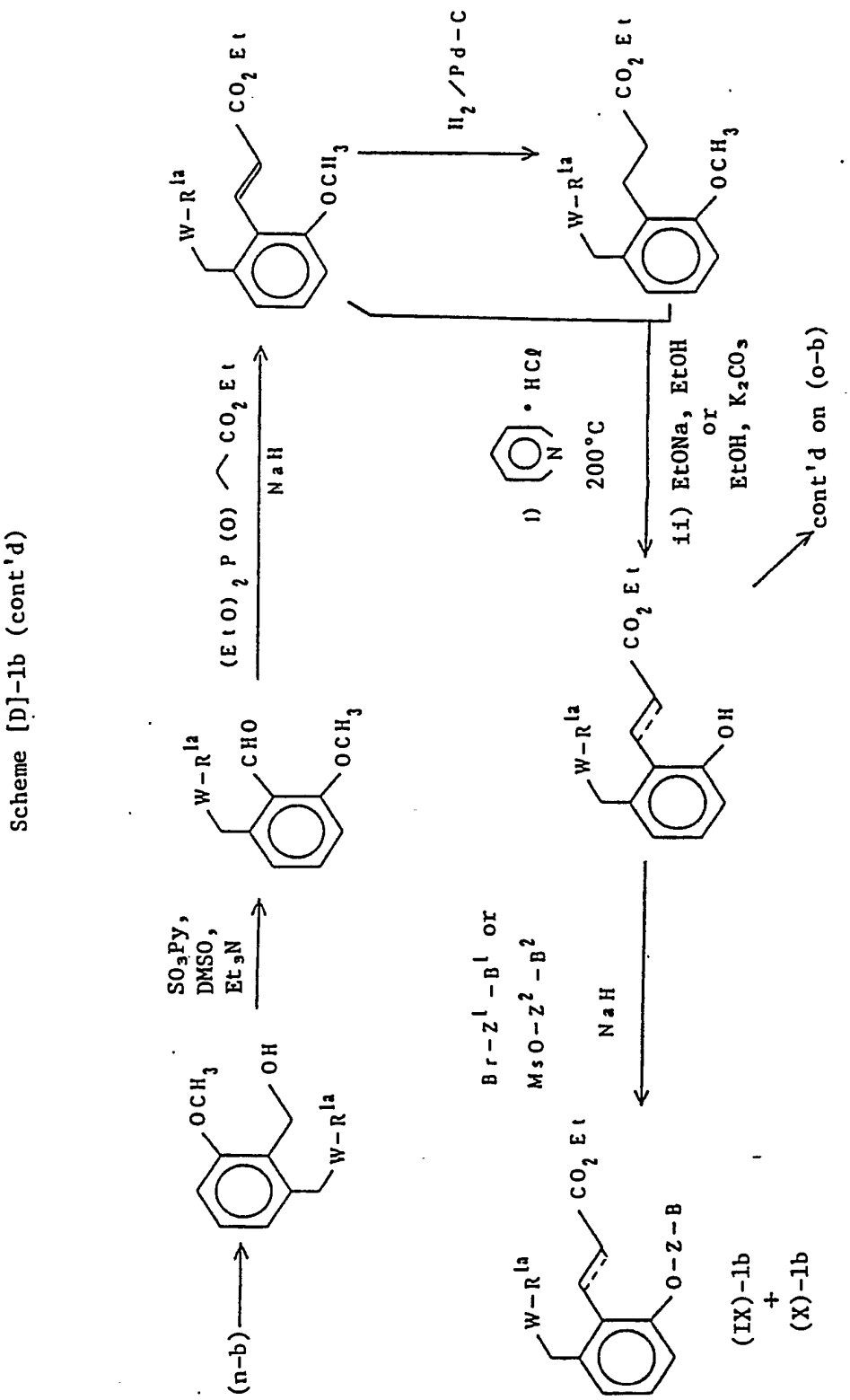
Scheme [C]-2b (cont'd)



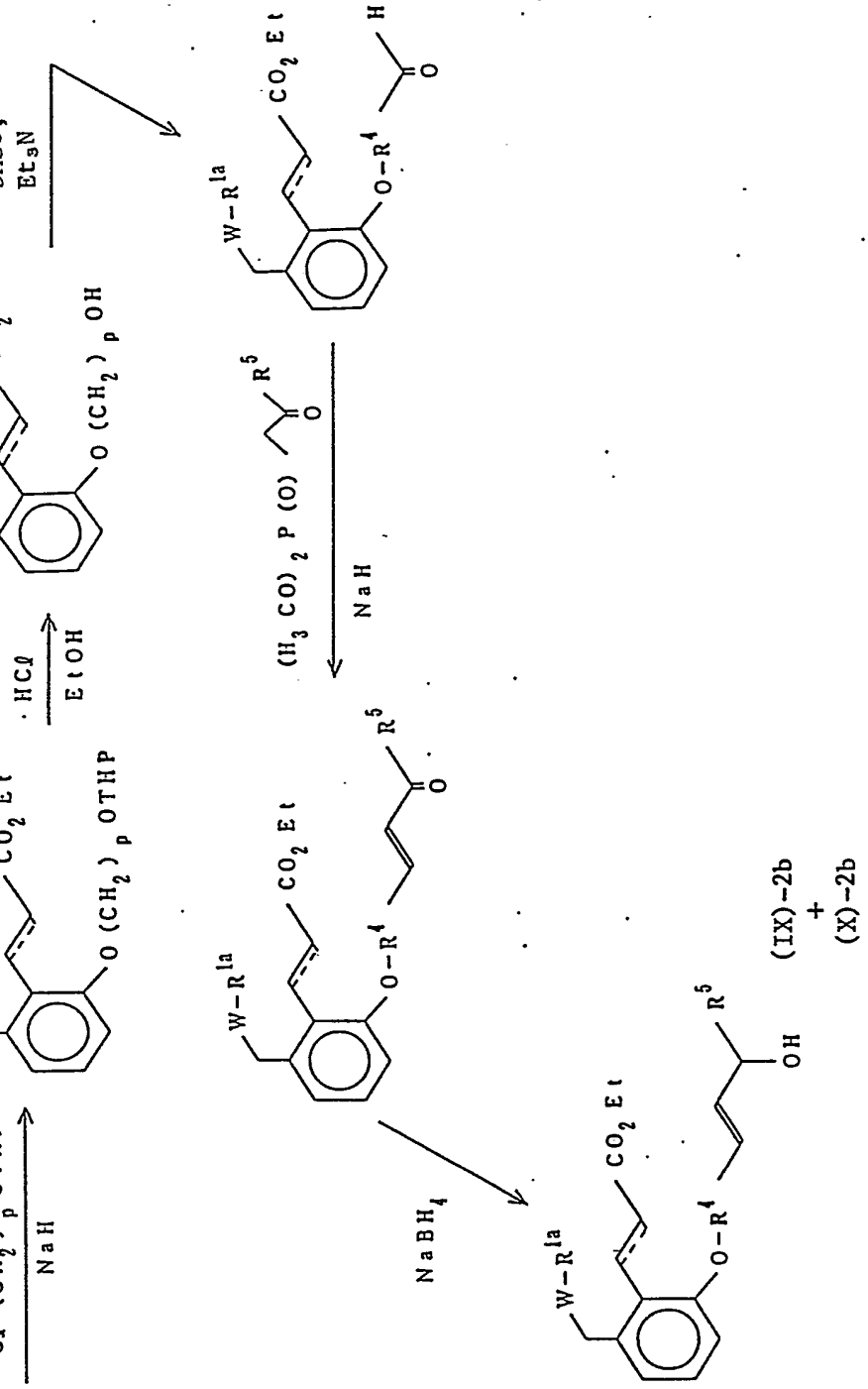
Scheme [D]-1b


DIBAL
NaBH4
CH2N2
t-BuOK
t-BuOK
H2/Pd-C
CH2N2
cont'd on (n-b)
cont'd on (p-b)

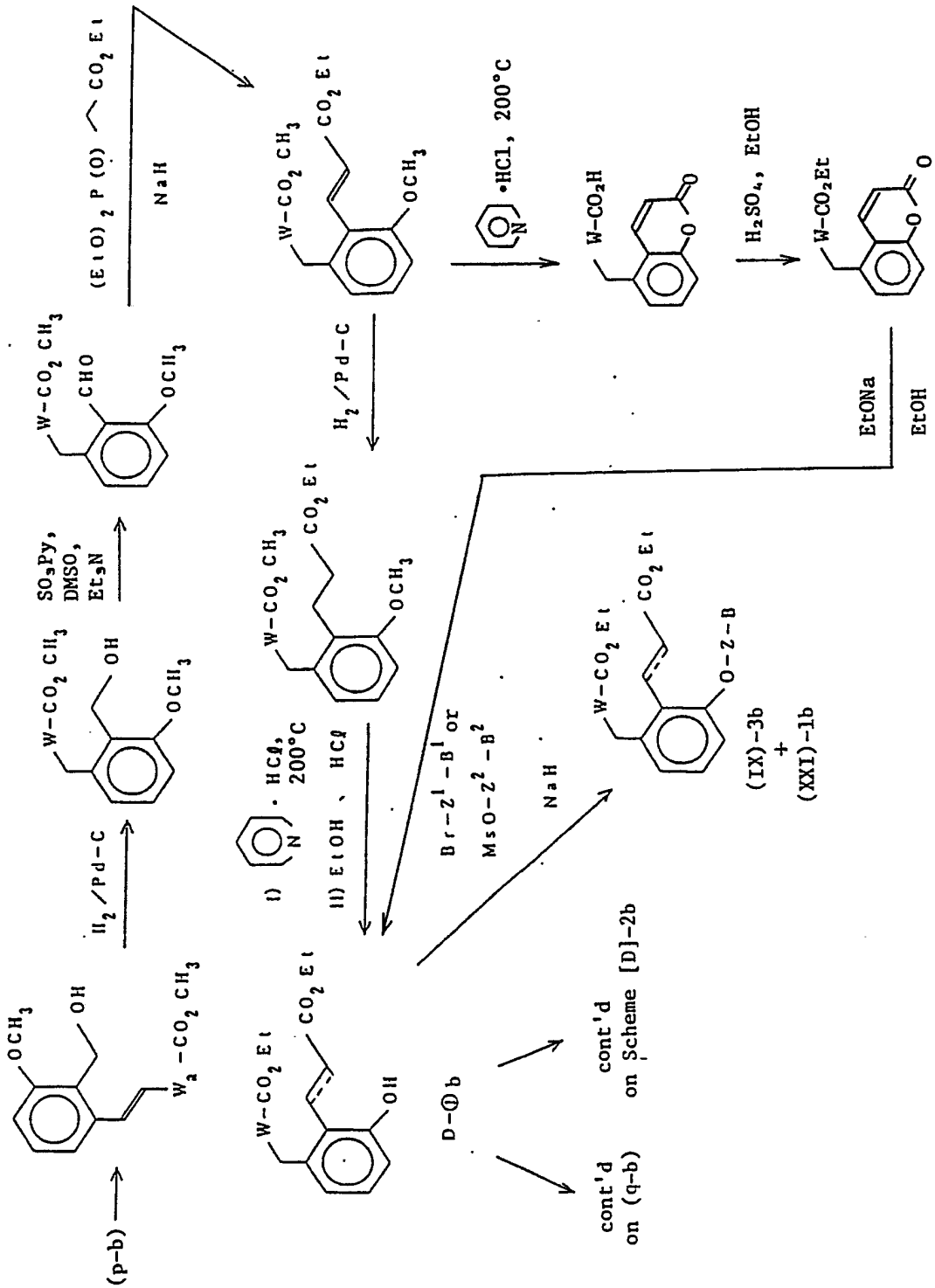
Scheme [D]-1b (cont'd)



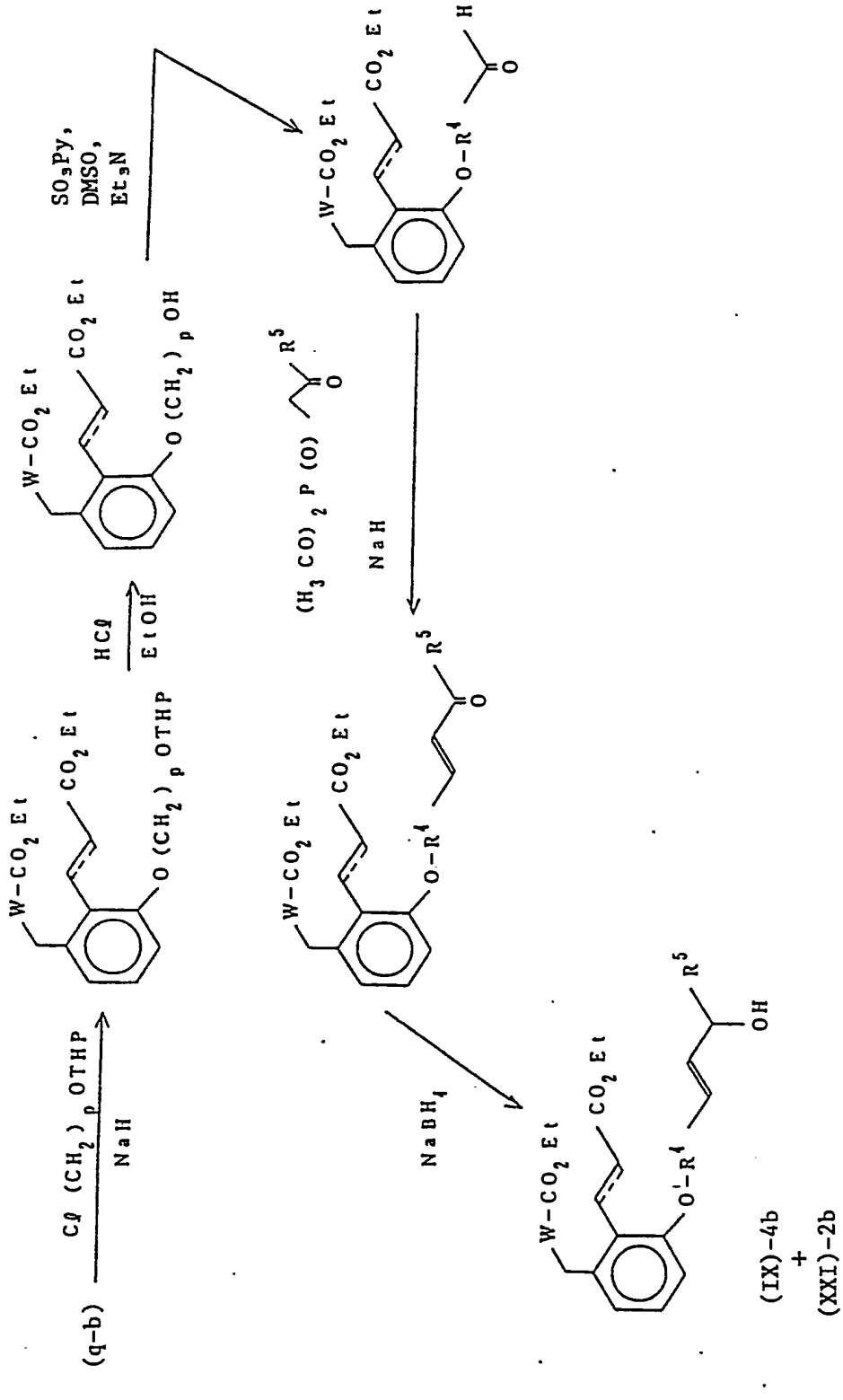
Scheme [D]-1b (cont'd)



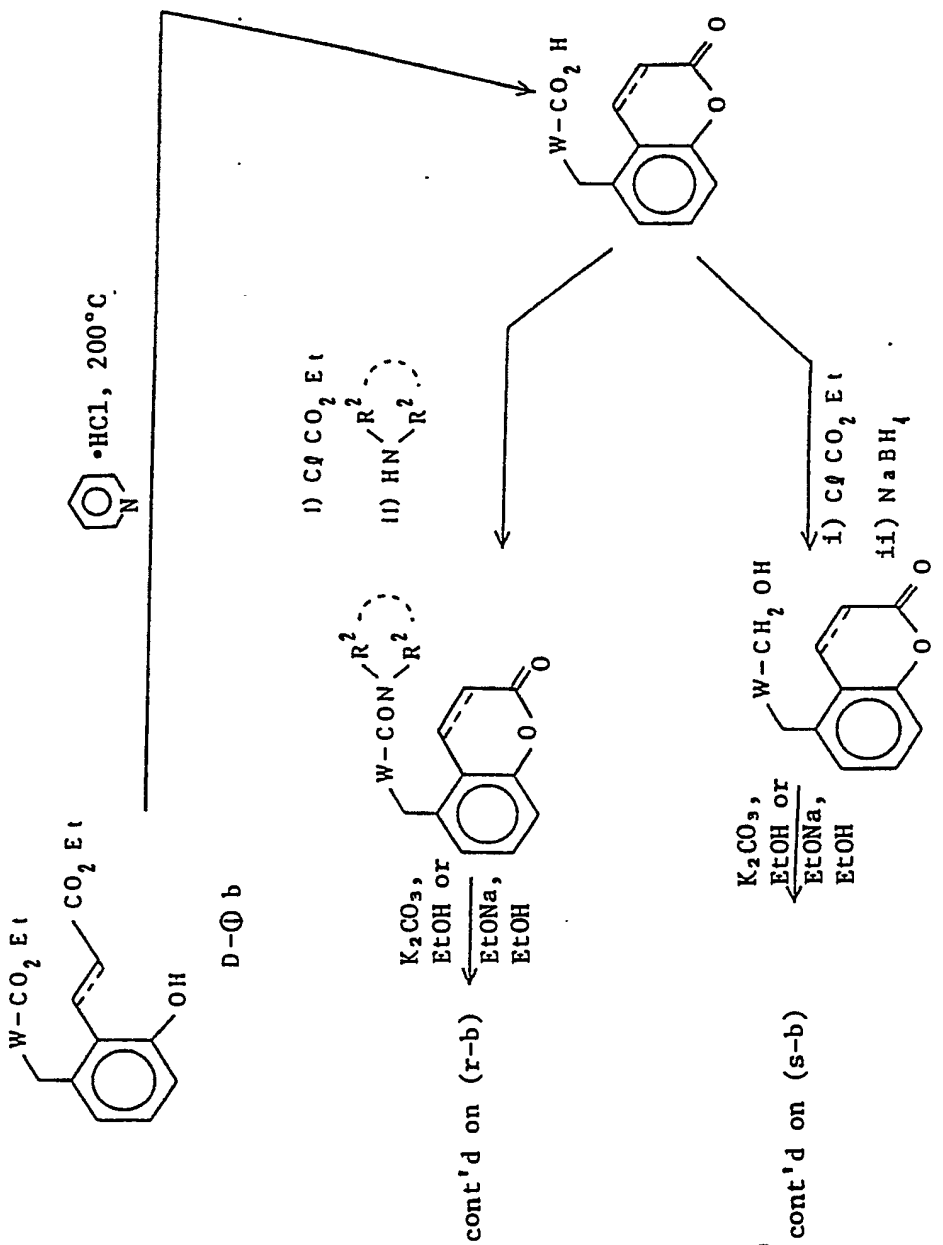
Scheme [D]-1b (cont'd)



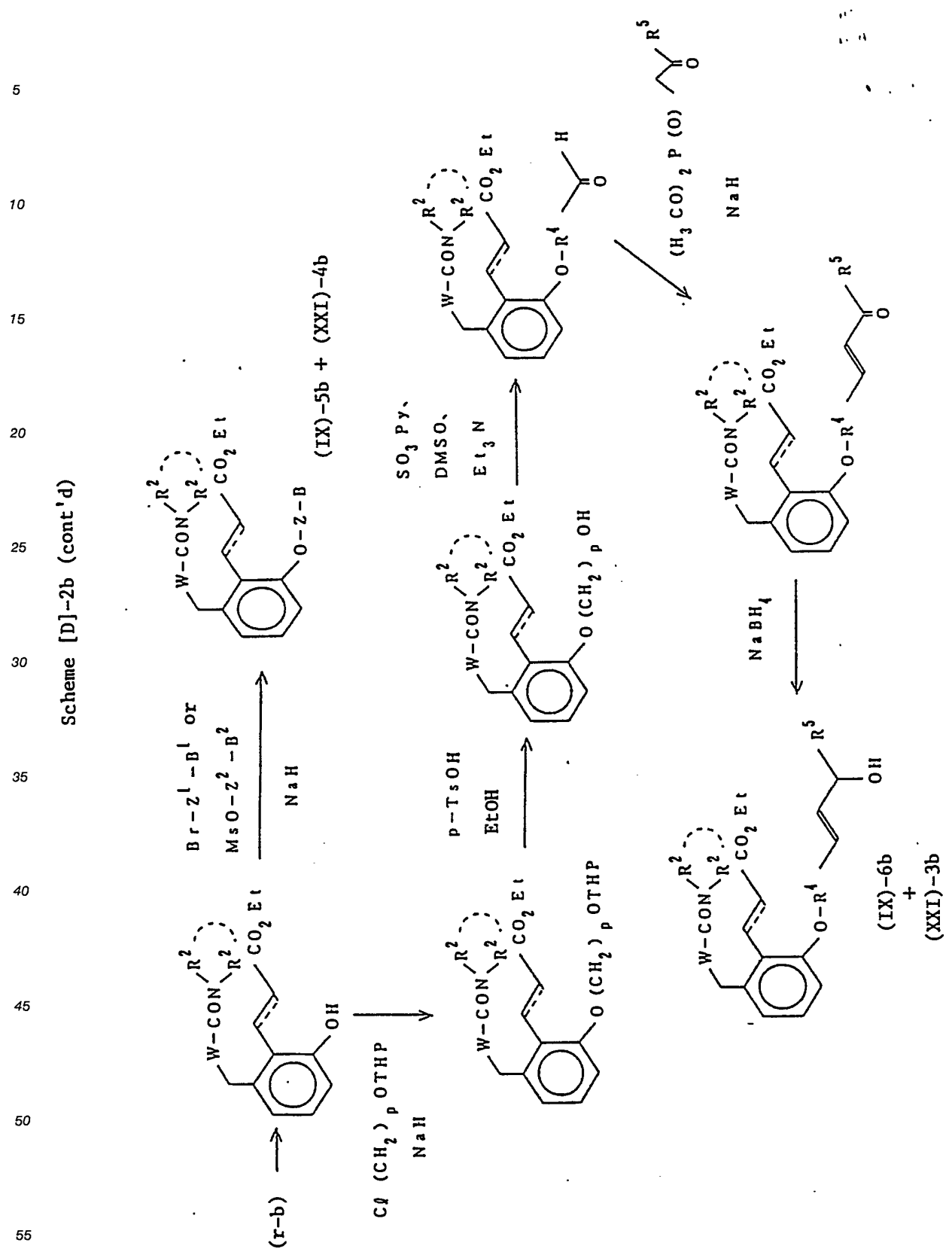
Scheme [D]-1b (cont'd)



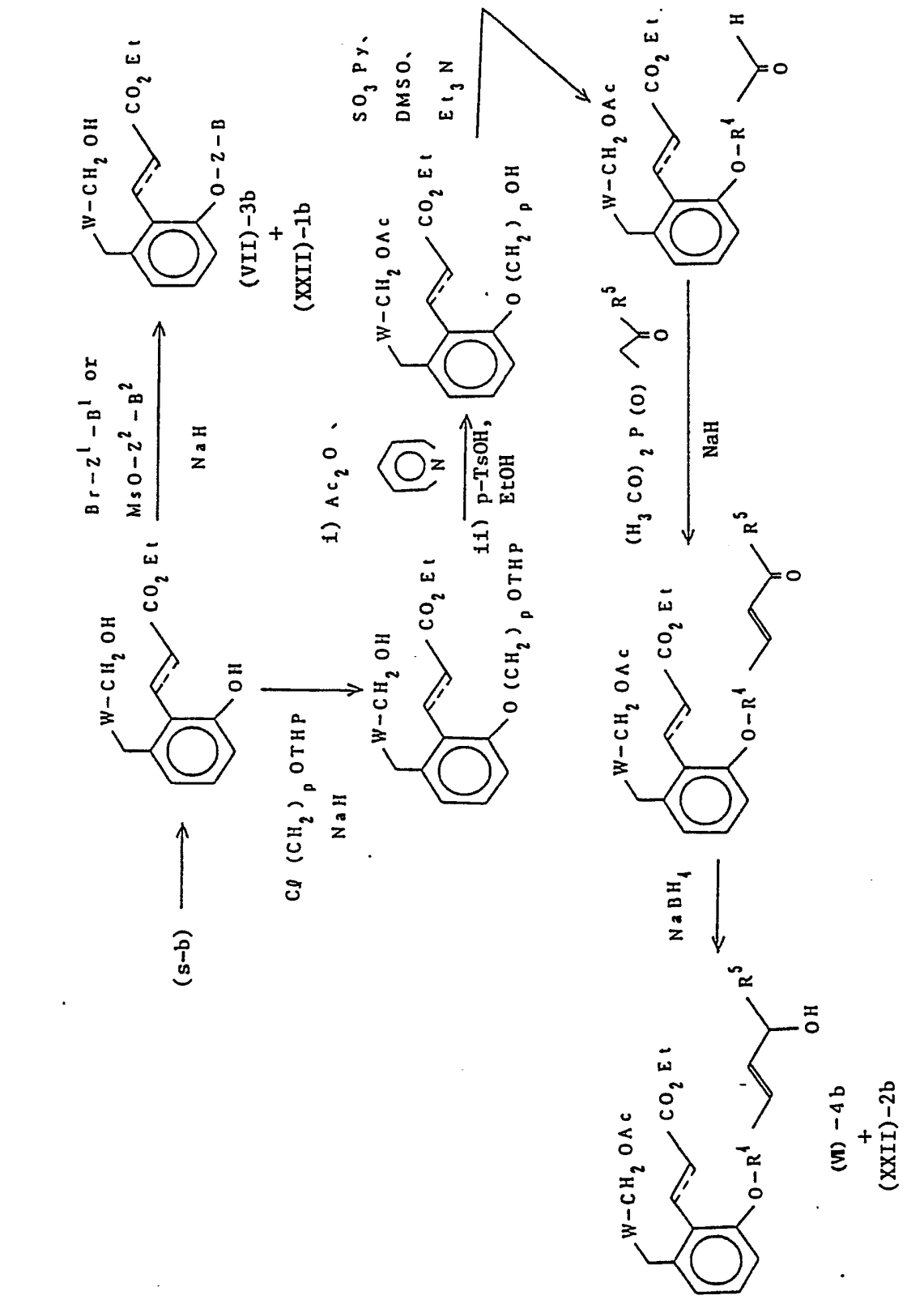
Scheme [D]-2b


•HCl, 200°C
D-① b
i) Cℓ CO2 Et
ii) HN
K2CO3, EtOH or EtONa, EtOH
cont'd on (r-b)
i) Cℓ CO2 Et
ii) NaBH4
K2CO3, EtOH or EtONa, EtOH
cont'd on (s-b)

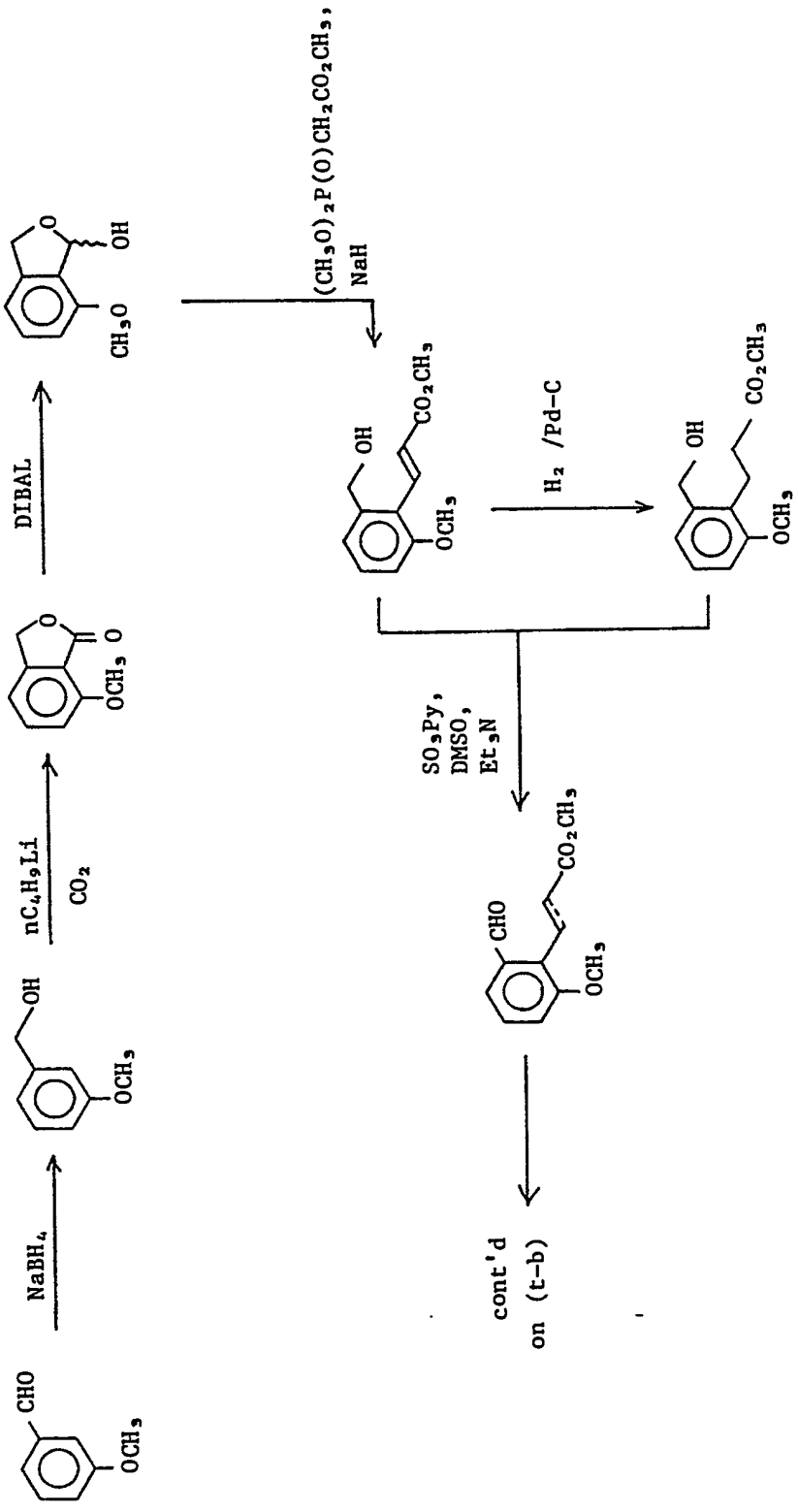
Scheme [D]-2b (cont'd)



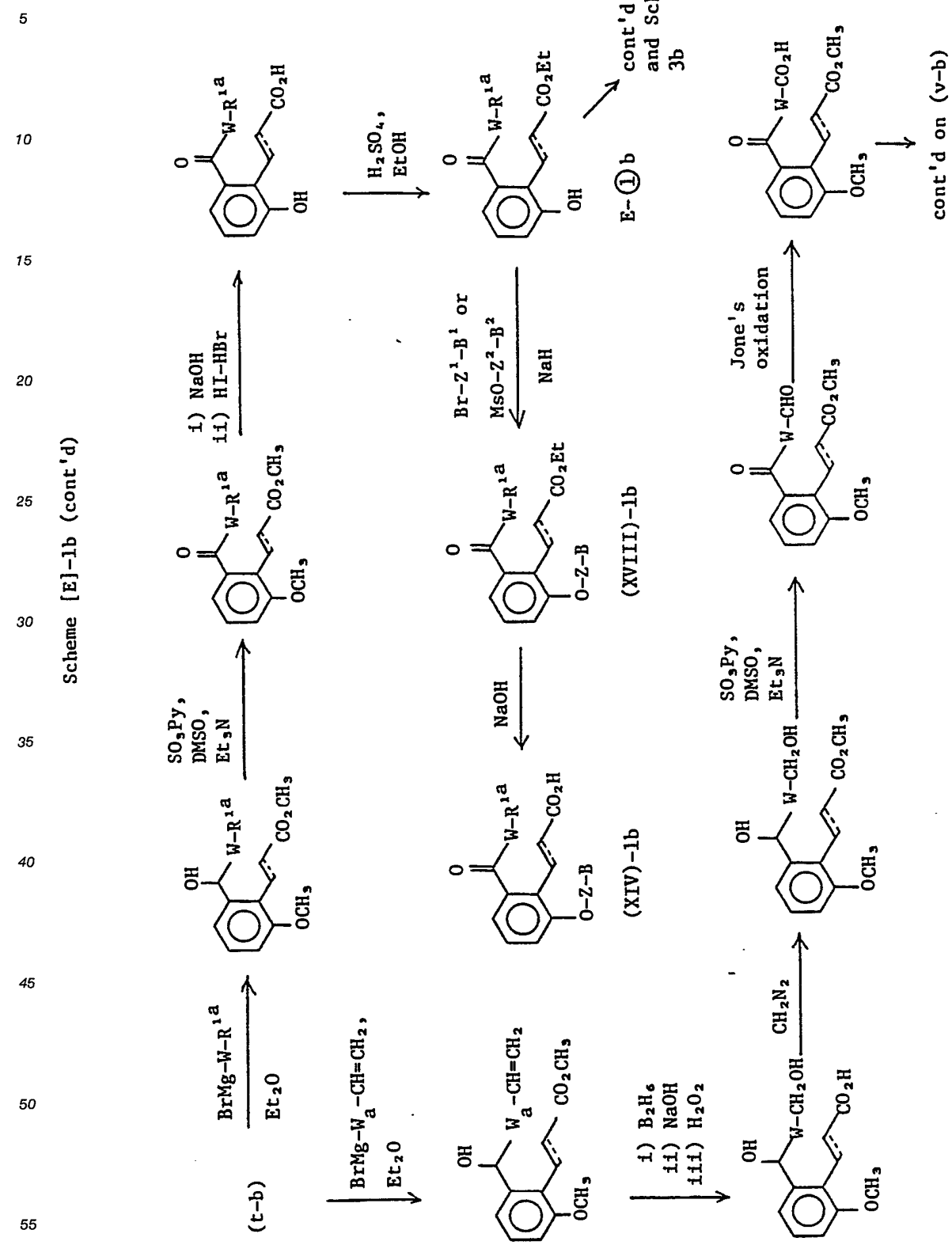
Scheme [D]-2b (cont'd)



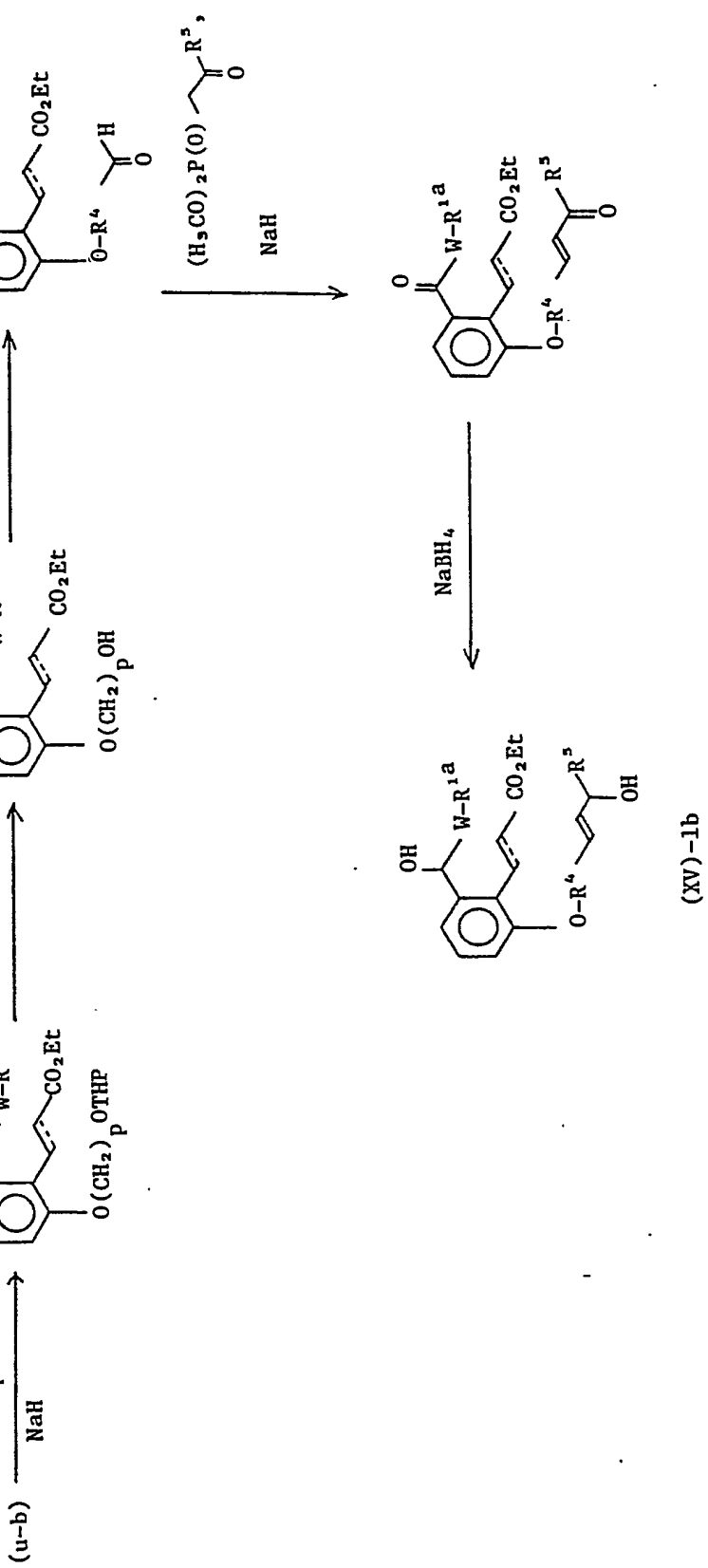
Scheme [E]-1b


CHO
OCH3
NaBH4
OH
OCH3
nC4H9Li
CO2
O
O
OCH3
DIBAL
O
OH
CH3O
(CH3O)2P(O)CH2CO2CH3,
NaH
OH
CO2CH3
OCH3
H2 /Pd-C
OH
CO2CH3
OCH3
SO3Py,
DMSO,
Et3N
CHO
CO2CH3
OCH3
cont'd
on (t-b)

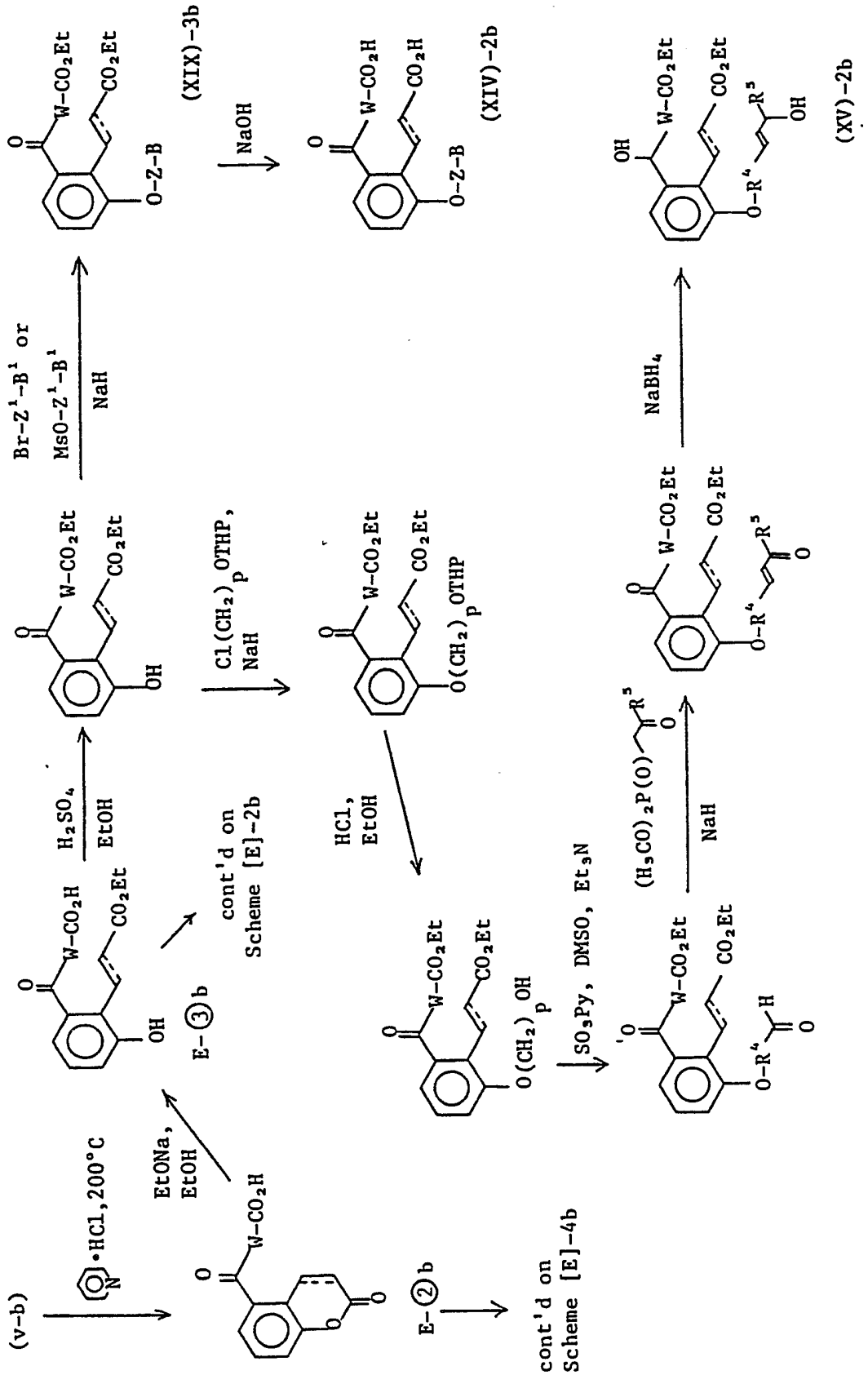
Scheme [E]-1b (cont'd)



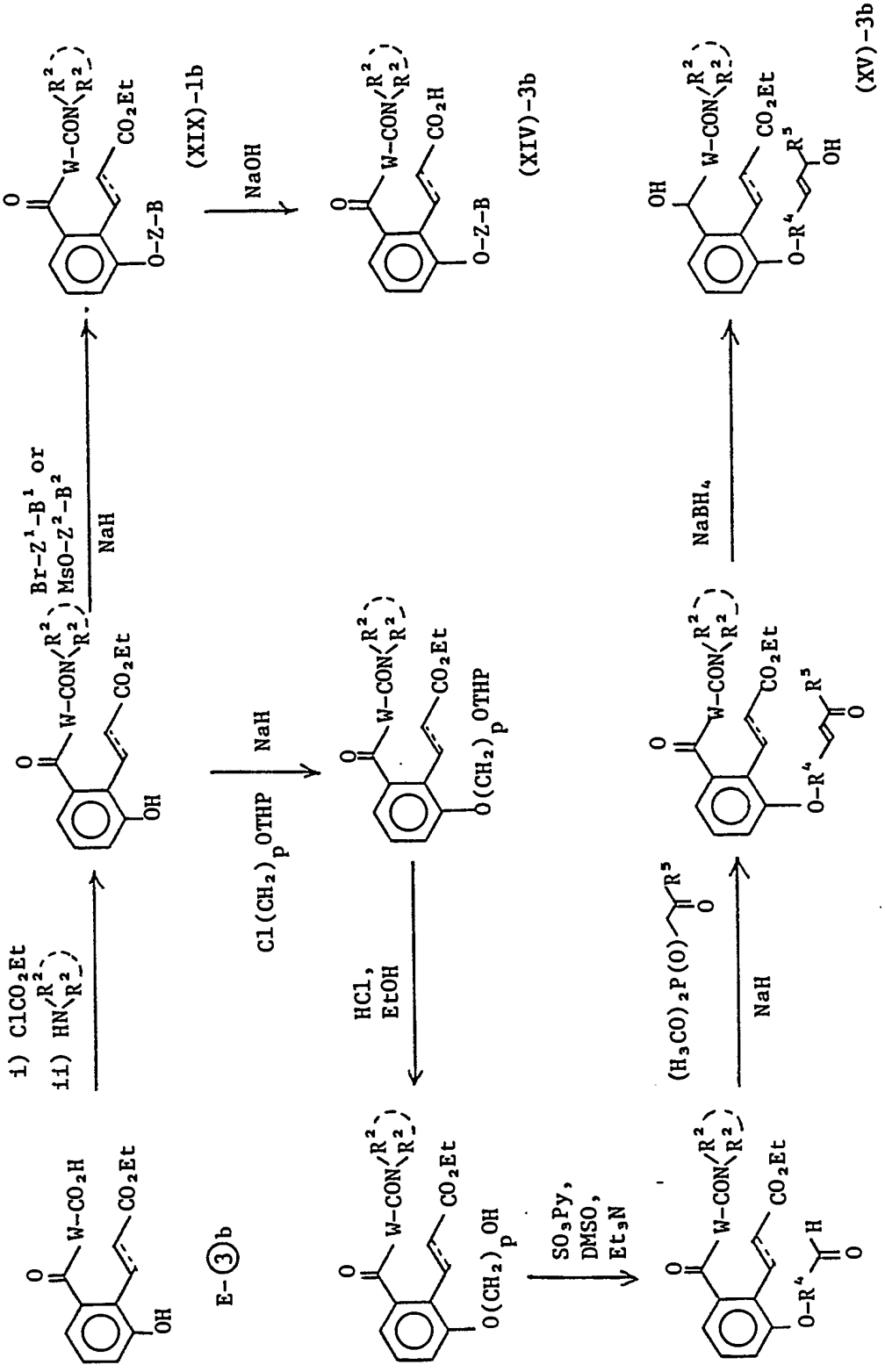
Scheme [E]-1b (cont'd)



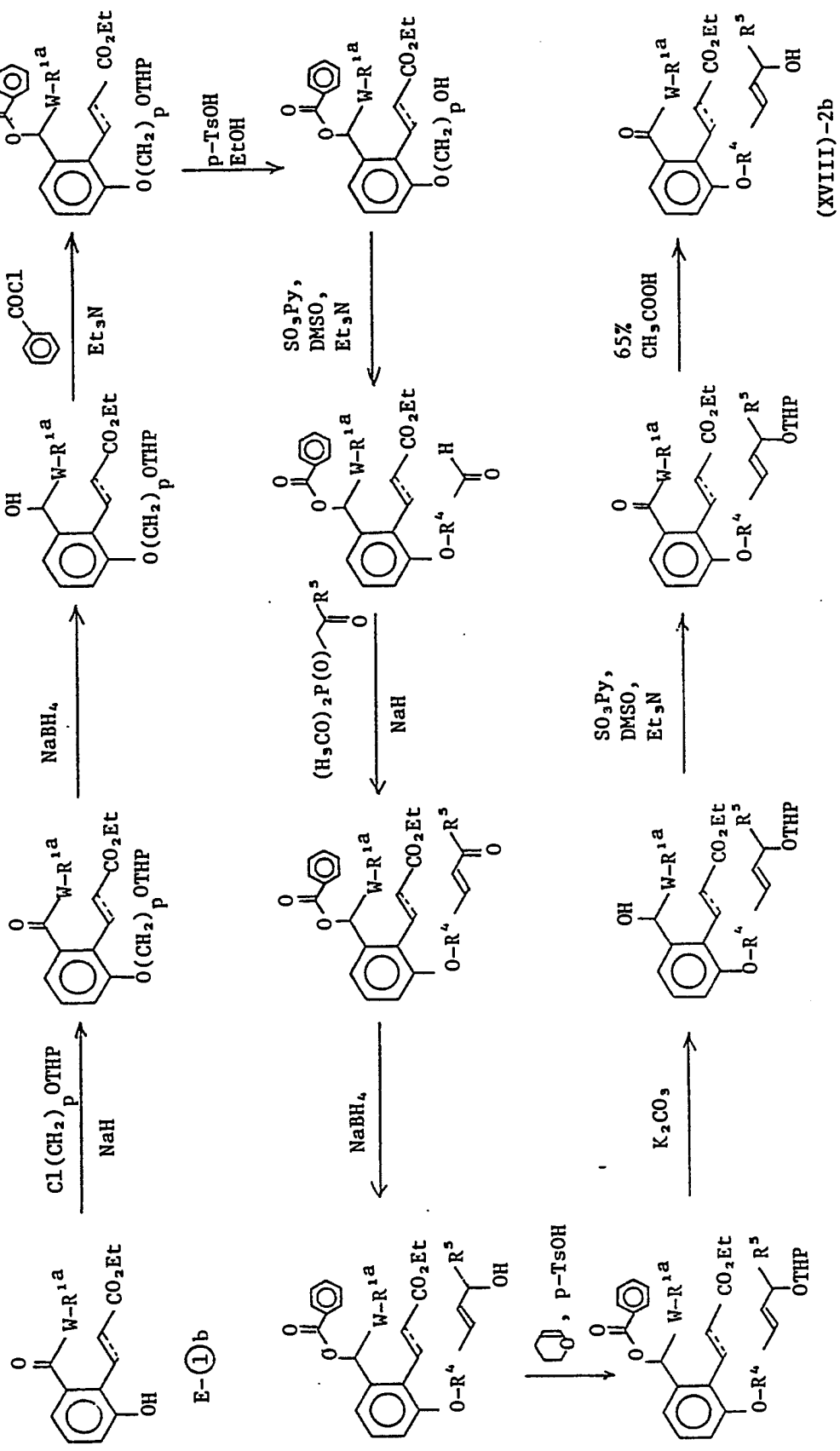
Scheme [E]-1b (cont'd)



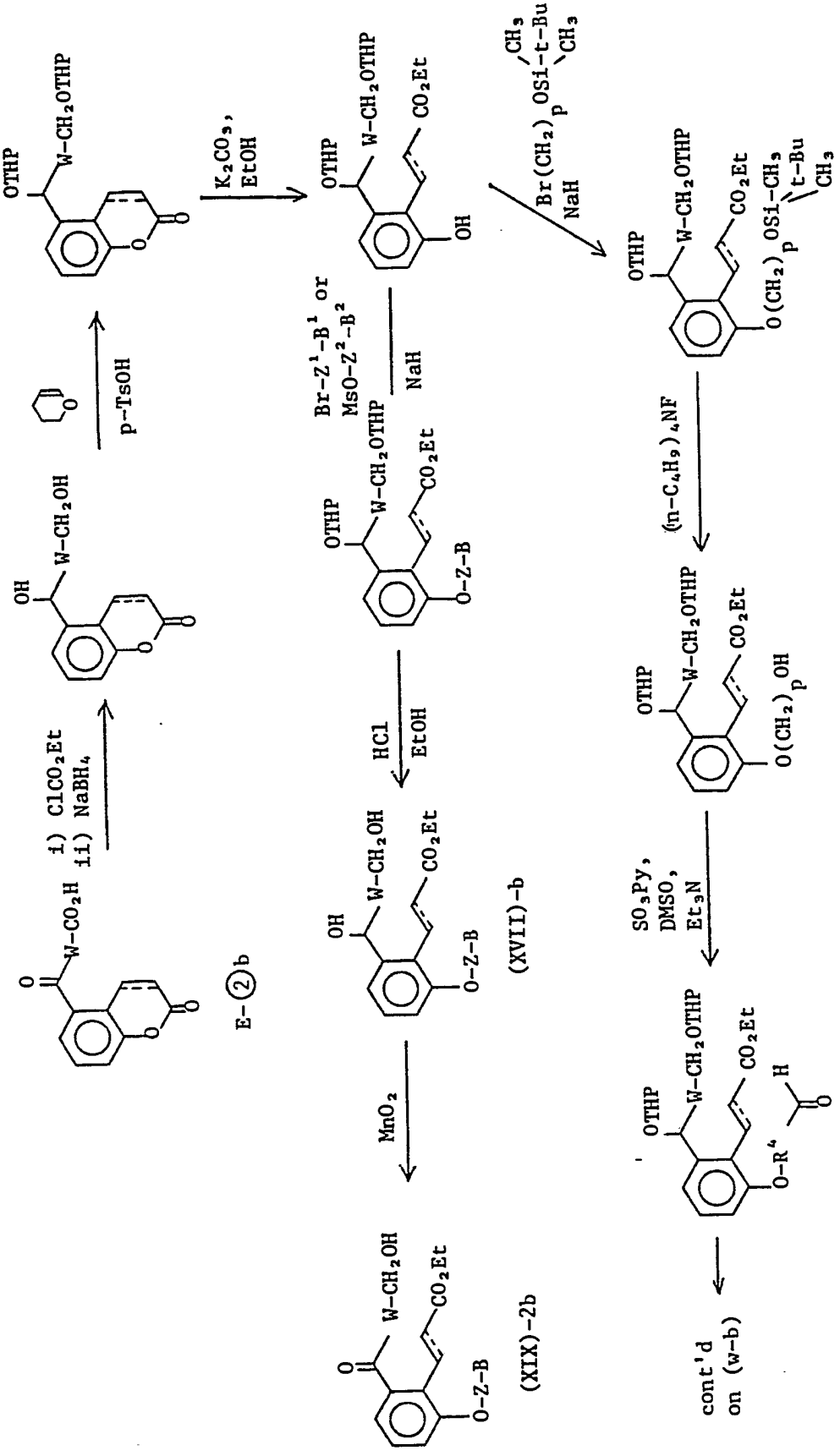
Scheme [E]-2b


i) ClCO2Et
ii) HN(R2)(R2)
Br-Z1-B1 or
MsO-Z2-B2
NaH
(XIX)-1b
NaOH
Cl(CH2)pOTHP
NaH
HCl,
EtOH
SO3Py,
DMSO,
Et3N
(H3CO)2P(O)
NaH
NaBH4
(XIV)-3b
(XV)-3b
E-③b

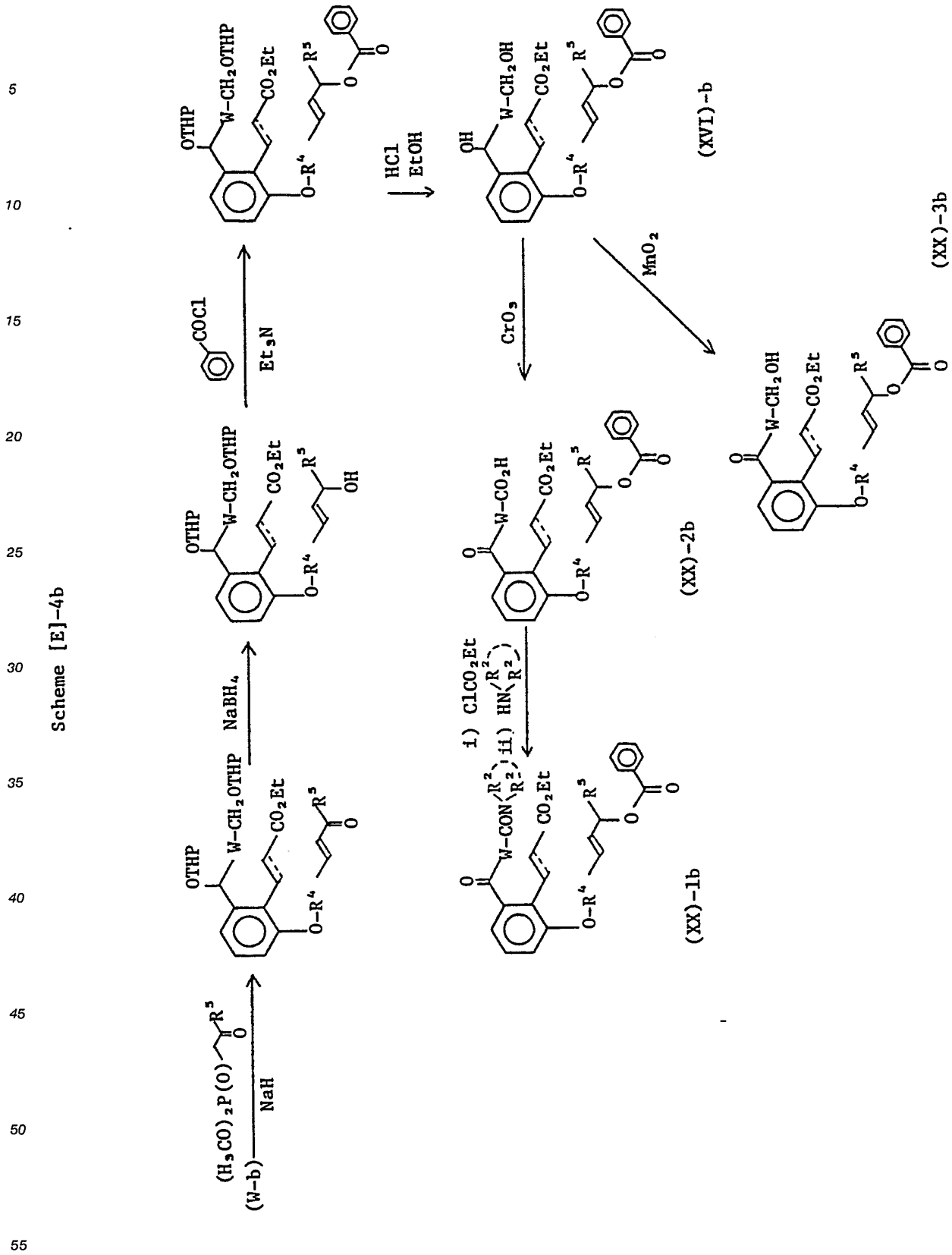
Scheme [E]-3b


E-①b
Cl(CH2)pOTHP
NaH
NaBH4
(H3CO)2P(O)
NaH
SO3Py,
DMSO,
Et3N
65%
CH3COOH
(XVIII)-2b
K2CO3
p-TsOH
p-TsOH
EtOH
COCl
Et3N
NaBH4
SO3Py,
DMSO,
Et3N

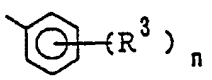
Scheme [E]-4b


E-②b
(XVII)-b
(XIX)-2b
cont'd on (w-b)
i) ClCO2Et ii) NaBH4
p-TsOH
K2CO3, EtOH
Br-Z1-B1 or MsO-Z2-B2
NaH
HCl EtOH
MnO2
Br(CH2)pOSi-t-Bu
NaH
(n-C4H9)4NF
SO3Py, DMSO, Et3N
OTHP
W-CH2OTHP
W-CH2OH
CO2Et
OH
O-Z-B
O(CH2)pOSi-CH3 t-Bu CH3
O(CH2)pOH
O-R4
H
O

Scheme [E]-4b


(H3CO)2P(O)
(W-b)
NaH
NaBH4
COCl
Et3N
HCl
EtOH
CrO3
MnO2
i) ClCO2Et
ii) HN
(XX)-1b
(XX)-2b
(XVI)-b
(XX)-3b

(In schemes,
R^{1a} is hydrogen,
saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom, which ring is unsubstituted or substituted by an oxo group, or C1-4 alkyl;
Z^1, taken together with B^1, is C3-22 alkyl;
Z^2 is C3-11 alkylene or alkenylene;
B^2 is the group shown by



;

p is 2-8;
r is 2 or 3;
THP is tetrahydropyran-2-yl;
Ms is mesyl;
Ac is acetyl;
p-TsOH is p-toluenesulfonic acid;
SO_3Py is the complex of sulfur trioxide and pyridine;
DMSO is dimethyl sulfoxide;
Py is pyridine;
DCC is 1,3-dicyclohexylcarbodiimide; and
the other symbols are the same meanings as described hereinbefore.)

In each reaction in the present specification, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

Starting materials

The starting materials and each reagents in the present invention are known or may be prepared by the known methods.

Effect

An antagonism on leukotriene B_4 of the compounds of the present invention has been confirmed by the following experimental results.

i) Binding affinity of ^{3}H-LTB_4 antagonist to human PMNL LTB_4 receptor

Human PMNLS (1×10^7 cells) were incubated with 1nM ^{3}H-LTB_4 in Hanks balanced salt solution (1 ml) at 4° C for 20 min. in the presence or absence of increasing concentrations of unlabeled LTB_4 or various compounds. Free ^{3}H-LTB_4 was separated from PMNLs-bound ligands by vacuum filteration through Whatman GF/B or C glass fiber filters. The filters were then washed rapidly 4 times with 2.5 ml of the ice-cold phosphate buffered saline. The radioactivity retained in the filter was determined by liquid scintillation counting. Specific binding was defined as the difference between total binding and binding in the presence of 3 μM LTB_4 (nonspecific binding). The inhibitory effect of specific ^{3}H-LTB_4 binding was calculated from the following equation.

The percentage of inhibition (%) = $100 - (B_1/B_0 \times 100)$
B_1 : specific ^{3}H-LTB_4 binding in presence of antagonist
B_0 : specific ^{3}H-LTB_4 binding in absence of antagonist

The results are shown in the following table 1.

Table 1

Ex. No. of the compounds	IC_{50} value (μM)	Ex. No. of the compounds	IC_{50} value (μM)
1	0.13	6 (c)	0.20
1 (a)	0.045	7 (a)	0.030
1 (c)	1.0	9	0.010
1 (e)	0.080	10	0.013
1 (f)	0.050	10 (c)	1.0
1 (i)	0.40	11	0.045
1 (j)	0.20	12	0.0070
1 (m)	0.49	12 (b)	0.0060
1 (n)	0.070	13	0.045
1 (o)	0.020	14	0.070
1 (q)	0.050	16	0.090
1 (r)	1.1	18	0.025
1 (s)	0.17	19	0.030
1 (t)	0.22	20	0.0036
1 (u)	0.080	29	0.018
2	0.040	30	0.016
2 (a)	0.20	30 (a)	0.070
2 (b)	0.020	30 (b)	0.15
3	0.17	31	0.040
3 (a)	0.20	31 (a)	0.015
4	0.090	32	0.050
4 (b)	0.060	33	0.015
5	0.020	34	0.020
5 (b)	0.30	35	0.20
5 (c)	0.70	36	0.15
5 (e)	0.35	37	0.0060
6	0.080	38	0.12
6 (b)	0.030	39	0.023
		40	0.17

ii) Inhibition of Human PMNLs aggregation

The purified human PMNLs were suspended in Hank's-0.5% BSA medium (pH 7.4) at 1 X 10^7 cells/ml. The PMNLs suspentions (200 μl) were preincubated with varying concentrations of tasted compounds for 3 min at 37° C prior to the addition of 10^{-8}M solution (10 ml) of LTB_4 in Hank's solution. PMNLs aggregation in vitro was performed with a multichannel platelet aggregometer. Aggregation was detected as change in light transmission with an aggregometer.

he results are shown in the following table 2.

Table 2

Ex. No. of the compounds	IC_{50} value (μM)	Ex. No. of the compounds	IC_{50} value (μM)
1 (a)	3.6	31	6.0
1 (o)	3.0	31 (a)	1.9
2 (b)	7.4	32	5.4
16	7.0	34	0.81
20	2.0	37	1.7
30	0.84	38	4.9
30 (a)	1.1		

The results in the Table 1 and Table 2 show that the compounds of the present invention possess an antagonism on leukotrine B_4.

Toxicity

It was confirmed that the toxicity of the compounds, of the present invention were very low. For example, the acute toxicity (LD_{50}) of the compounds in Example 30 and 31(a) are 3.9 g/kg and 2.2 g/kg, respectivity, in oral administration and 175 mg/kg and 260 mg/kg, respectivity, in intravenous administration in mouse. Accordingly, it was confirmed that the compounds of the present invention were useful for pharmaceutical agent.

Application for Pharmaceuticals

The compounds of the formula (I), of the present invention, are useful for prevention and/or treatment for allergic dermatosis, rheumatism, gout, psoriasis, arthritis, trychophytosis, cardiac infarction etc. in mammals including human beings since they possess an antagonism on LTB_4

For the purpose above described, the compounds, of the formula (I), of the present invention and non-toxic salts thereof may be normally by administered systemically or partially usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc.. In the human adult, the doses per person per dose are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 1 mg and 100 mg, by parenteral administration up to several times per day, or contineous administration between 1 and 24 hrs. per day from vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

When administration of the compounds of the present invention, it is used as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules contain hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent (lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate etc.) The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (magnesium stearate etc.), disintegrating agents (cellulose calcium glycolate etc.), stabilizing agent (lactose etc.), and assisting agent for dissolving (glutamic acid, asparaginic acid etc.).

The tablets or pills may, if desired, be coated with film of gastric or enteric material (sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate etc.), or be coated with more than two films. And further, it may be include capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs.

In such compositions, one or more of the active compound(s) is or are comprise in inert diluent(s) commonly used in the art (purified water, ethanol etc.).

Besides inert diluents, such compositions may also comprise adjuvants (wetting agents, suspending agent etc.), sweetening agents, flavouring agents, perfuming agents and preserving agent.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfite etc.), isoionic bufier (sodium chloride, sodium citrate, citric acid etc.)

For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one more of active compound(s) is or are admixed at least one of inert aqueous diluent(s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSOLBATE80 (registered trade mark) etc.).

Injections may comprise aditional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose etc.), assisting agents such as assisting agents for dissolving (glutamic acid, asparaginic acid etc.).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactures in the form of sterile solid compositions, for example, by freeze-drying, and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

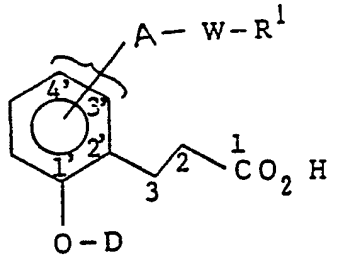
Other compositions for parenteral administration include liquids for external use, and endermic liniments (ointment etc.), suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

Reference example and examples

The following reference examples and examples are illustrated the present invention, but not limit the present invention.

The solvents in the parentheses show the eluting or developing solvents and the ratios of the solvents used are by volume in chromatographic separations. Unless otherwise specified, "IR" was measured by the KBr tablet method and "NMR" was measured in a mixture of chloroform-d and methanol-d_4, respectively.

The compounds of the formula (I) can be named as derivatives of an alkan(en)oic acid with the numbering of the benzene ring as follows:

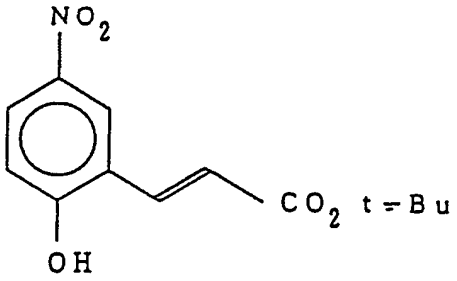


(when Y is ethylene)

The above compound can be called 3-(1-substituted-(3 or 4)-substitutedbenzen-2-yl)propionic acid.

Reference example 1

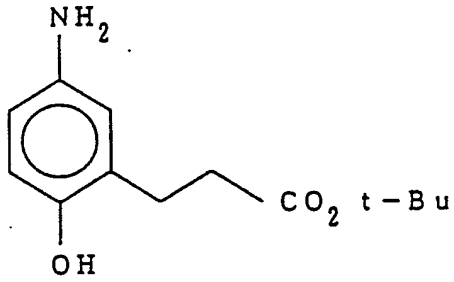
t-Butyl 3-(2-hydroxy-5-nitrophenyl)-2E-acrylate



Sodium hydride (content:62%, 3.3g) was suspended in tetrahydrofuran (30 ml). The suspension was ice-cooled in an atmosphere of argon gas. A solution of t-butyl diethylphosphonoacetate (20.9 g) in tetrahydrofuran (20 ml) was added to the suspension. The mixture was stirred for 15 min. at room temperature. A solution of 2-hydroxy-5-nitrobenzaldehyde (6.6 g) in tetrahydrofuran (20 ml) was gradually added to the mixture often with ice-cooling. The mixture was stirred for 10 min. at room temperature. Acetic acid was gradually added to the mixture until pH of the mixture was down to 5.0. The reaction mixture was gel-filtered with using YMC gel. Moreover the gel was washed with ethyl acetate. A mixture of the filtrate and washings was evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1 → 3 : 2) to give the title compound (10.0 g) having the following physical data.
TLC(n-hexane : ethyl acetate = 3 : 2) : Rf 0.40.

Reference example 2

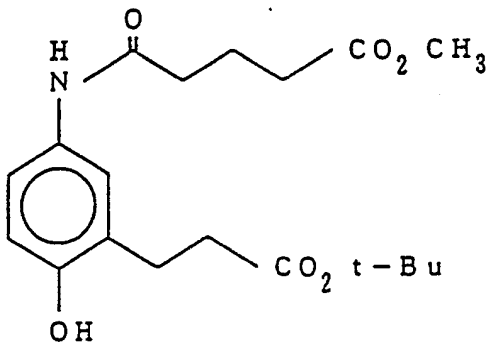
t-Butyl 3-(2-hydroxy-5-aminophenyl)propionate



The unsaturated ester (prepared in reference example 1 : 8.0 g) was dissolved in ethanol (100 ml). A suspension of 10% Palladium-Carbon (1.0 g) in ethanol (10 ml) was added to the solution. The mixture was stirred for 2 hr. at room temperature under an atmosphere of hydrogen gas. The reaction solution was filtered with using Celite 545. Celite was washed with ethanol. The mixture of the filtrate and washings was evaporated to give the residue (7.1 g), containing the title compound having the following physical data. The residue was used in next reaction without purification.
TLC(n-hexane : ethyl acetate = 3 : 2) : Rf 0.22.

Reference example 3

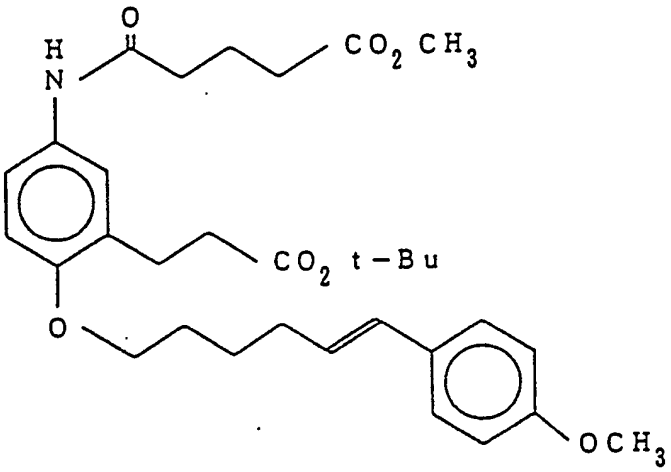
t-Butyl 3-[1-hydroxy-4-(4-methoxycarbonylbutanamido)benzen-2-yl]propionate



The ester (prepared in reference example 2; 6.4 g) was dissolved in methylene chloride (100 ml). Pyridine (5.0 ml) was added to the solution. 4-methoxycarbonylbutanoyl chloride (3.75 ml) was added to the solution with ice-cooling. The mixture was stirred for 10 min. at room temperature. Ice was added to the reaction mixture. The mixture was extracted with ethyl acetate. The extract was washed with 2N hydrochloric acid, saturated aqueous solution of sodium bicarbonate, followed by saturated brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 3 → 3 : 8) to give the title compound (9.6 g) having the following physical data.
TLC(n-hexane : ethyl acetate = 2 : 3) : Rf 0.51.

Reference example 4

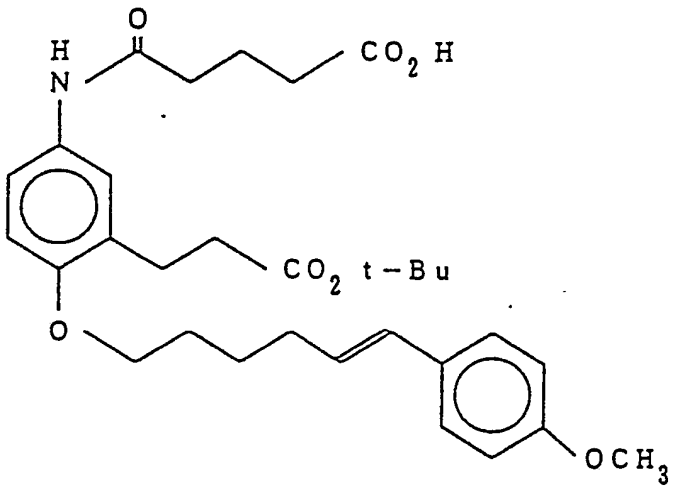
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4- (4-methoxycarbonylbutanamido)benzen-2-yl]propionate



Phenol (580 mg; prepared in reference example 3) and sodium hydride (content : 62%, 62 mg) were dissolved in dried dimethylformamide (2 ml). The solution was stirred at room temperature in an atmosphere of argon gas. A solution of 6-(p-methoxyphenyl)-5E-hexenol methanesulfonate (450 mg) in dried dimethylformamide (1 ml) was added to the solution. The mixture was stirred for 2 hr. at 60 °C. The reaction mixture was poured into a mixture of ice and 1N hydrochloric acid (10 ml). The mixture was extracted with diethyl ether - ethyl acetate (1 : 1). The extract was washed with water, saturated aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 3 : 2) to give the title compound (265 mg) having the following physical data.
TLC(n-hexane : ethyl acetate = 1 : 2) : Rf 0.30.

Reference example 5

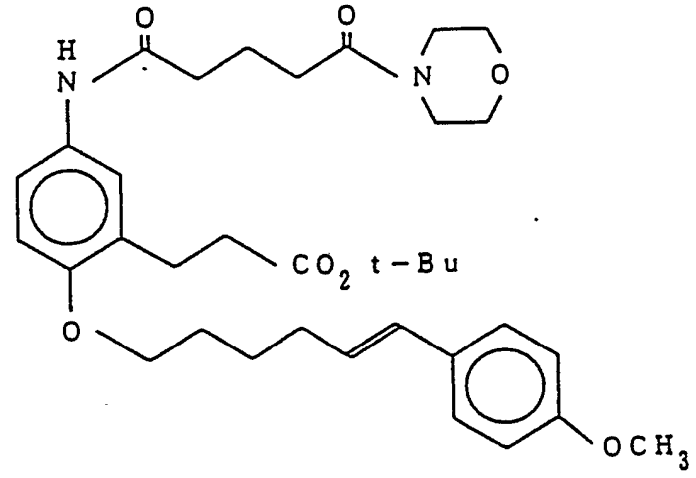
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(4-carboxylbutanamido)benzen-2-yl]propionate.



The ester (265 mg; prepared in reference example 4) was dissolved in a mixture of methanol (3 ml) and tetrahydrofuran (2 ml). A 1N aqueous solution of sodium hydroxide (1.0 ml) was added to the solution. The solution was stirred for 3 hr at room temperature. The reaction solution was diluted with water. 1N hydrochloric acid (1.5 ml) was added to the solution. The mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and evaporated to give the residue contained the title compound having the following physical data. The residue was used in next reaction without purification.
TLC(ethyl acetate) : Rf 0.10.

Reference example 6

t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(5-oxo-5-morpholinopentanamido)benzen-2-yl]-propionate



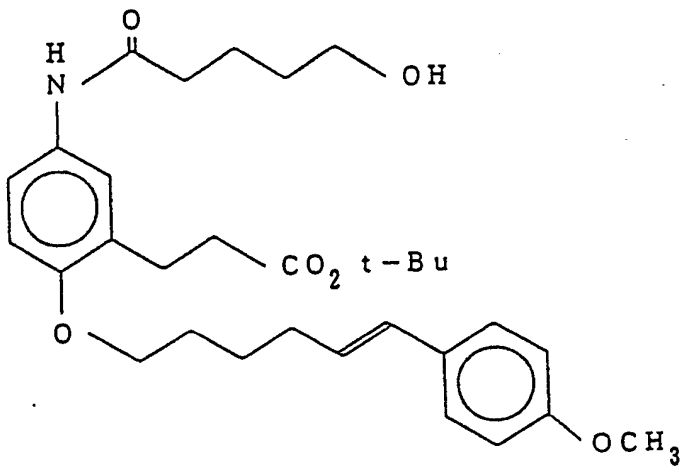
The ester (86 mg; prepared in reference example 5) was dissolved in a mixture of dried tetrahydrofuran (1 ml) and triethylamine (44 μl). Ethyl chloroformate (23 μl) was gradually added to the solution at -10 °C. The solution was stirred for 15 min. at -10 °C. Morpholine (generally 0.5 ml) was added to the solution. The mixture was stirred for 30 min. at 0 °C and then for 30 min. at room temperature. The reaction mixture was poured to a mixture of ice and 2N hydrochloric acid (10 ml). The mixture was extracted with ethyl acetate. The extract was washed with 2N hydrochloric acid, water, an aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate) to give the title compound (74 mg) having the following physical data.

TLC(ethyl acetate) : Rf 0.10;
MS : m/z 608(M^+), 552, 184, 156, 121.

Reference example 7

t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(5-hydroxypentanamido)benzen-2-yl]propionate

]

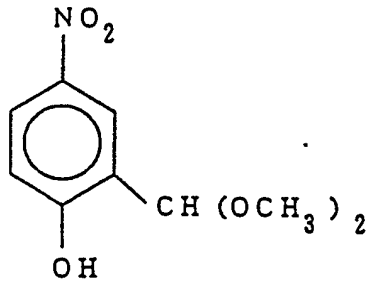


The ester (210 mg ; prepared in reference example 5) was dissolved in tetrahydrofuran (2 ml). Triethylamine (56 μl) was added to the solution. Ethyl chloroformate (35 μl) was added to the solution at -10 °. The solution was stirred for 10 min. at -10 °C. Sodium borohydride (25 mg) and methanol (0.3 ml) was gradually added to a half quantity of the reaction solution. The solution was stirred for 15 min.. The reaction solution was diluted with ethyl acetate. The solution was washed with 1N hydrochloric acid, saturated aqueous solution of sodium bicarbonate, followed by saturated brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 1 : 2 → 1 : 3) to give the title compound (51 mg) having the following physical data.

TLC(n-hexane : ethyl acetate = 1 : 2) : Rf 0.32;
MS : m/z 511 (M^+), 455.

Reference example 8

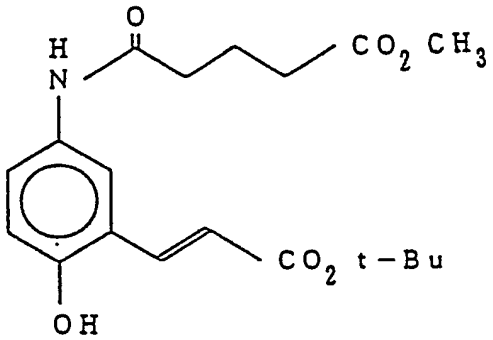
1-Hydroxy-2-dimethoxymethyl-4-nitrobenzene



2-Hydroxy-5-nitrobenzaldehyde (3.34 g) was dissolved in methanol (30 ml). Trimethyl orthoformate (20 ml) and then Dowex 50W X 8 (H^+ form)(generally 2 ml) were added to this solution. The mixture was stirred for 30 min. at room temperature. The resin was removed from the reaction mixture by passing the mixture through an alumina. The filtrate was evaporated to give the title compound (4.0 g) having the following physical data.
TLC(n-hexane : ethyl acetate = 2 : 1) : Rf 0.21;
MS : m/z 2/3 (M^+), 195, 181.

Reference example 9

t-Butyl 3-[1-hydroxy-4-(4-methoxycarbonylbutanamido)benzen-2-yl]-2E-acrylate

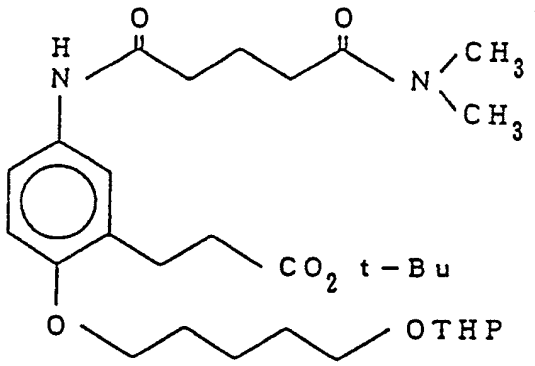


The amide (853 mg), which was obtained with using the acetal (549 mg; prepared in reference example 8) by the same procedure as reference example 2 → reference example 3, was dissolved in 5% hydrous acetone (10 ml). p-Toluenesulfonic acid (100 mg) was added to the solution. The solution was stirred for 1 hr. at room temperature. The reaction solution was diluted with ethyl acetate. The solution was washed with saturated aqueous solution of sodium bicarbonate, followed by saturated brine, dried over anhydrous magnesium sulfate and then evaporated. The residue was recrystallized from n-hexane - ethyl acetate (= 1 : 1) to give the corresponding aldehyde (711 mg).

Sodium hydride (content : 62%; 110 mg) was suspended to tetrahydrofuran (10 ml). The suspension was ice-cooled in an atmosphere of argon gas. A solution of t-butyl diethylphosphonoacetate (700 mg) in tetrahydrofuran (15 ml) was added to the suspension. The mixture was stirred for 15 min. at room temperature. A solution of the obtained aldehyde (711 mg) in tetrahydrofuran (10 ml) was gradually added to the mixture occasionally with ice-cooling. The mixture was stirred for 10 min. at room temperature. Acetic acid was gradually added to the reaction mixture until pH of the reaction mixture was down to 5.0. The reaction mixture was gel-filtered with using YMC gel. Moreover the gel was washed with ethyl acetate. A mixture of the filtrate and washings was evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 1 : 3) to give the title compound (179 mg) having the following physical data.
TLC(n-hexane : ethyl acetate = 1 : 4) : Rf 0.40.

Reference example 10

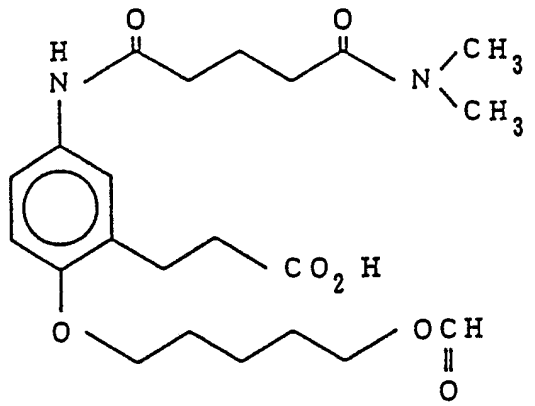
t-Butyl 3-[1-[5-(tetrahydropyran-2-yl)oxy-n-pentyl]oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate



The phenol compound (356 mg), which was obtained with using the ester prepared in reference example 3 by the same procedure as reference examples 5 → reference example 6 (with the proviso that dimethylamine was used instead of morpholine), was dissolved in dimethyl formamide (5 ml). The solution was ice-cooled. Sodium hydride (content : 62%; 22.6 mg) was added to the solution. This solution was stirred for 15 minutes at room temperature. A solution of 1-chloro-5-(tetrahydropyran-2-yl)oxy-n-pentane (206 mg) in dimethyl formamide (1 ml) was added to the reaction mixture. The mixture was stirred at 75 ° C all night. The reaction mixture was diluted with ether. The mixture was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (336 mg) having the following physical data.
MS: m/z 548 (M^+), 464.

Reference example 11

3-[1-(5-formyloxy-n-pentyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionic acid

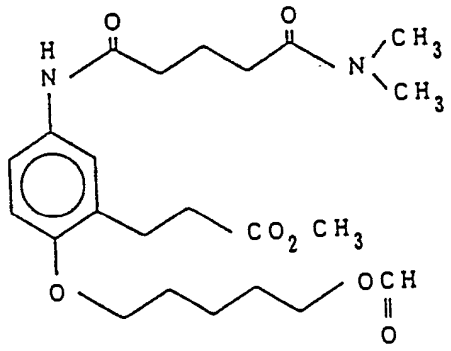


The ester (336 mg) prepared in reference example 10 was dissolved in formic acid (5 ml). The solution was stirred for 1 hr. at room temperature and then for 1 hr. at 45 ° C. The reaction solution was evaporated to give the residue contained the title compound having the following physical data. The residue was used

in next reaction without purification.
TLC(chloroform : methanol = 10 : 1) : Rf 0.33

Reference example 12

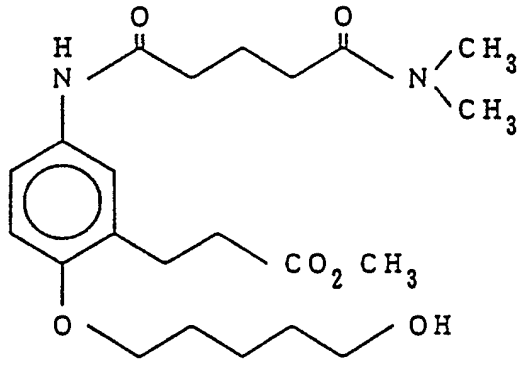
Methyl 3-[1-(5-formyloxy-n-pentyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate



The residue which contained the carboxylic acid prepared in reference example 11 was dissolved in ethyl acetate (2 ml). A solution of diazomethane in ether was added to the solution until the reaction mixture was slightly tinged with yellow. The reaction mixture was evaporated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (227 mg) having the following physical data.
MS : m/z 450 (M^+), 406.

Reference example 13

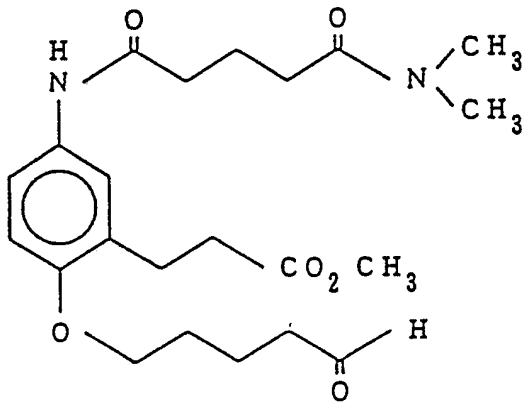
Methyl 3-[1-(5-hydroxy-n-pentyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate



The ester (220 mg) prepared in reference example 12 was dissolved in methanol (2 ml). Potassium carbonate (82.8 mg) was added to the solution. The mixture was stirred for 2 hr. at room temperature. The mixture was acidified with 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (176 mg) having the following physical data.
MS : m/z 422(M^+), 281.

Reference example 14

Methyl 3-[1-(4-formyl-n-butyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate

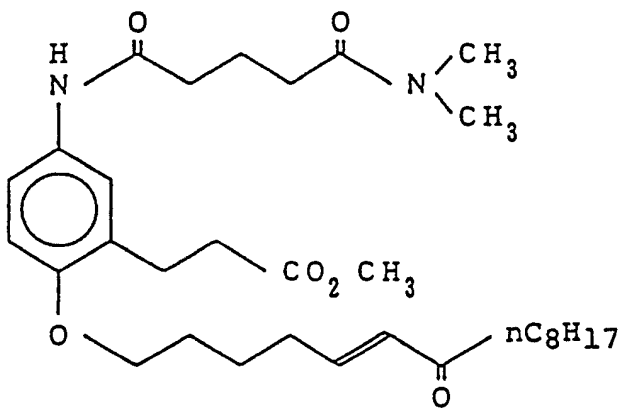


The alcohol (173 mg) prepared in reference example 13 was dissolved in dimethyl sulfoxide (2 ml). Triethylamine (207.5 mg) and sulfur trioxide-pyridine complex (195.6 mg) were added to the solution. The mixture was stirred for 30 min. at room temperature. The reaction solution was acidified with 1N hydrochloric acid. The solution was extracted with ether. The extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by colomn chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (61 mg) having the following physical data.

NMR: δ 9.80 (1H, t, J=1Hz), 8.10 (1H, s), 7.42 (1H, d,d, J = 8Hz, J=1Hz), 7.23 (1H, d, J=1Hz), 6.75 (1H, d, J=8Hz), 4.00-3.90 (2H, m), 3.70 (3H, s), 3.03 (3H, s), 2.99 (3H, s), 2.92 (2H, t, J=7Hz), 2.65-2.40 (6H, m), 2.15-1.95 (2H, m), 1.90-1.45 (4H, m).

Reference example 15

Methyl 3-[1-(5E-7-oxopentadecenyl)oxy-4-(4-dimethylaminocarbonylbutylamido)benzen-2-yl]propionate

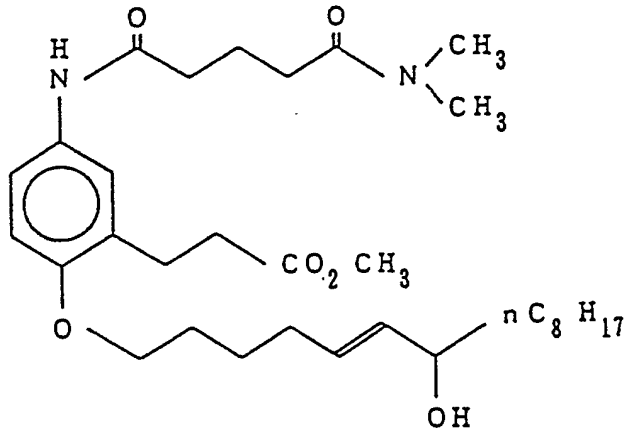


A solution of dimetyl 2-oxodecylphosphonate (132 mg) in tetrahydrofuran (1 ml) was added to a suspension of sodium hydride (content : 62%; 7.75 mg) in tetrahydrofuran (3 ml). A solution of the aldehyde

(59 mg) prepared in reference example 14 in tetrahydrofuran (2 ml) was added to the mixture. The solution was stirred for 30 min. at room temperature and then for 1 hr. at 60°C. The reaction solution was acidified with acetic acid. The solution was gel-filtered. The filtrate was evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : methanol = 20 : 1) to give the title compound (50 mg) having the following physical data.
MS : m/z 558 (M^+), 417.

Reference example 16

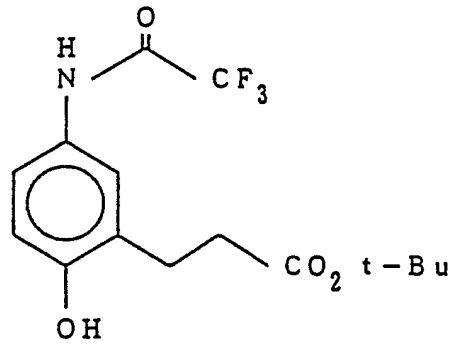
Methyl 3-[1-(5E-7-hydroxypentadecenyl)oxy-4-(4-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate



The compound (48 mg) prepared in reference example 15 and cerium chloride•$7H_2O$ (37.3 mg) were dissolved in methanol (1 ml). Sodium borohydride (3.25 mg) in limited amounts was added to the solution. The mixture was stirred for 30 min. at room temperature. The reaction solution was acidified with acetic acid. The solution was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (46 mg) having the following physical data.
MS : m/z 560, 542.

Reference example 17

t-Butyl 3-(1-hydroxy-4-trifluoroacetoamidobenzen-2-yl)propionate



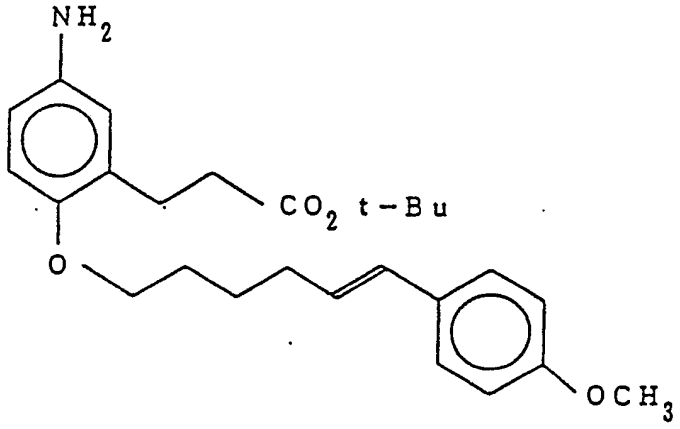
t-Butyl 3-(1-hydroxy-4-aminobenzen-2-yl)propionate was dissolved in a mixture of tetrahydrofuran (100 ml) and triethylamine (7.1 ml). Anhydrous trifluoroacetic acid (6.0 ml) was added to the solution at 0 °C in an atmosphere of argon gas. The solution was stirred for 2 hr. at 0 °C. The reaction solution was poured into a mixture of ice and 1N hydrochloric acid (100 ml). The reaction mixture was extracted with ethyl acetate (300 ml). The extract was washed with water, saturated aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from a mixture of ethyl acetate-n-hexane (1 : 5) to give the title compound having the following physical data.

TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.30;

MS : m/z 333 (M^+), 277, 259, 231, 217.

Reference example 18

t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-aminobenzen-2-yl]propionate



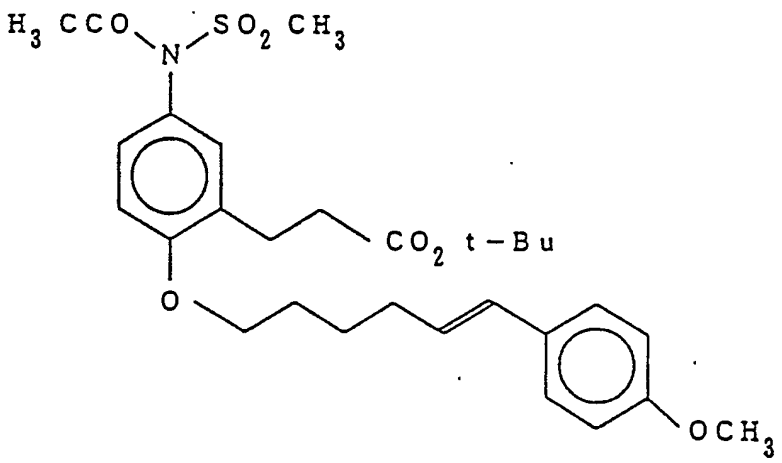
The trifluoroacetoamide (5.3 g), which was prepared with using the compound prepared in reference example 17 by the same procedure as reference example 4 was dissolved in a mixture of methanol (30 ml) and water (5 ml). Anhydrous potassium carbonate (2.8 g) was added to the solution. The mixture was stirred at room temperature a whole day and night. Water (100 ml) was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (200 ml x 2). The extract was washed with brine, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 2 : 3) to give the title compound (3.5 g) having the following physical data.

TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.20;

MS : m/z 425 (M^+), 369, 189, 181, 163, 147, 121.

Reference example 19

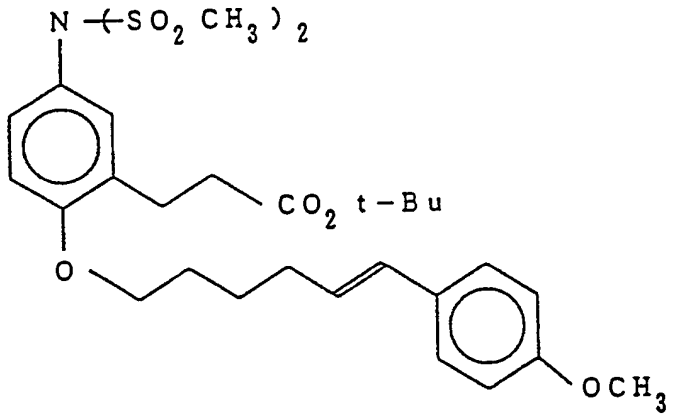
t-Butyl 3-[1-(6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(N-acetyl-N-mesylaminobenzen-2-yl]propionate



The ester (176 mg) prepared in reference example 18 was dissolved in a mixture of methylene chloride (3 ml) and triethylamine (0.29 ml). Methanesulfonyl chloride (35 µl) was added to the solution at 0 °C. The solution was stirred for 30 min. Acetyl chloride (0.12 ml) was added to the reaction solution. The mixture was refluxed for 10 min. The reaction mixture was poured into a mixture of ice and 1N hydrochloric acid (10 ml). The reaction mixture was extracted with ethyl acetate (80 ml). The extract was washed with water, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 2) to give the title compound (200 mg) having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 1) : Rf 0.40;
MS : m/z 545 (M^+), 489, 447, 189, 147, 121.

Reference example 20

t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-dimesylaminobenzene-2-yl]propionate

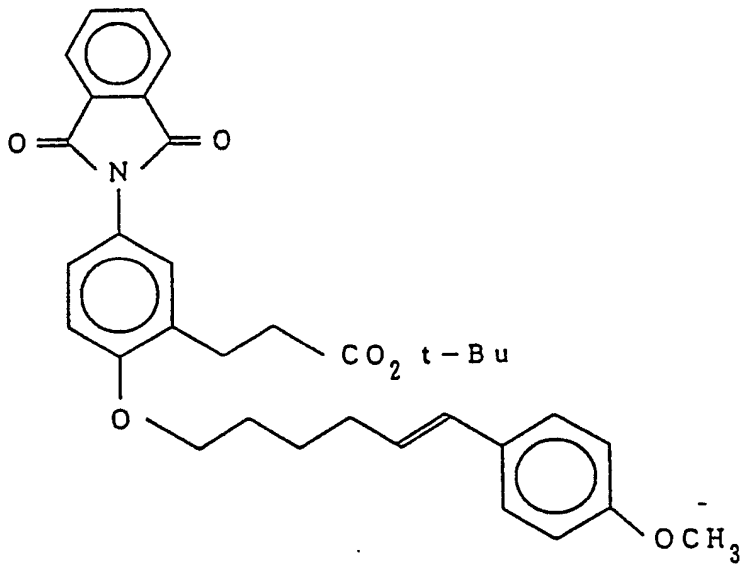


The ester (158 mg) prepared in reference example 18 was dissolved in a mixture of methylene chloride (3 ml) and triethylamine (0.15 ml). Methanesulfonyl chloride (72 µl) was added to the solution at room temperature. The solution was stirred for 1 hr. The reaction solution was poured into a mixture of ice and 1N hydrochloric acid (10 ml). The reaction mixture was extracted with ethyl acetate (80 ml). The extract was washed with water, followed by brine, dried over anhydrous mangesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 2) to give the

title compound (170 mg) having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.25;
MS : m/z 581 (M^+), 525, 189, 147, 121.

Reference example 21

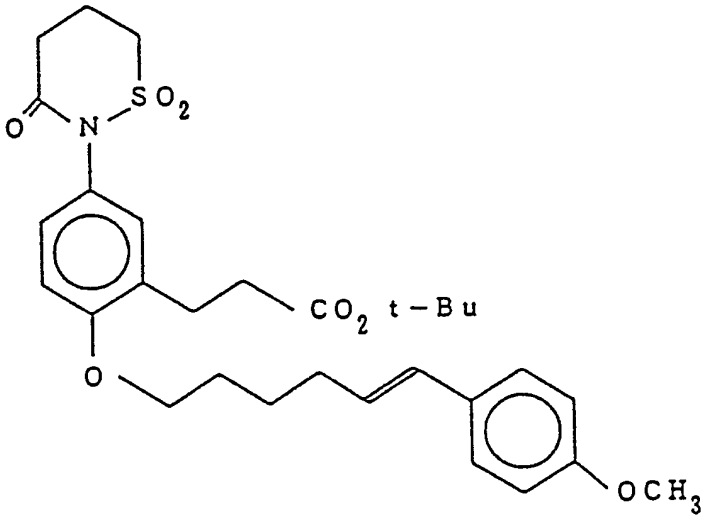
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-phthalimidobenzen-2-yl]propionate



The ester (176 mg) prepared in reference example 18 was dissolved in chloroform (5 ml). Anhydrous phthalic acid (120 mg) was added to the solution. The solution was refluxed for 24 hr. The reaction solution was evaporated. The residue was purified by column chromatography on silica gel (methylene chloride → methylene chloride : ethyl acetate = 10 : 1) to give the title compound (130 mg) having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 4) : Rf 0.20;
MS : m/z 555 (M^+), 499, 311, 293, 189, 147, 121.

Reference example 22

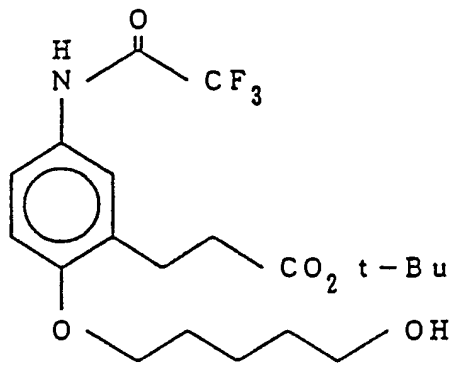
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(perhydro-1,2-thiazin-1,1,3-trione-2-yl)benzen-2-yl]-propionate



The t-butyl ester (950 mg), which was prepared with using the ester prepared in reference example 18 by the same procedure as reference example 3 (with the proviso that the corresponding sulfonyl chloride was used instead of 4-methoxycarbonylbutanoyl chloride) → reference example 5, was dissolved in a mixture of tetrahydrofuran (15 ml) and triethylamine (0.69 ml). Ethyl chloroformate (0.24 ml) was gradually added to the solution at 15° C in an atmosphere of argon gas. The solution was stirred for 10 min at -15° C and then for 30 min at 0° C. The reaction solution was poured into a mixture of ice and 1N hydrochloric acid (20 ml). The reaction mixture was extracted with ethyl acetate (100 ml). The extract was washed with water, saturated aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 2 : 1) to give the title compound (710 mg) having the following physical data.
TLC(ethyl acetate : n-hexane = 2 : 1) : Rf 0.60;
MS : m/z 557 (M^+), 501, 187, 121.

Reference example 23

t-Butyl 3-[1-(5-hydroxy-n-pentyl)oxy-4-trifluoroacetoamidobenzen-2-yl]propionate

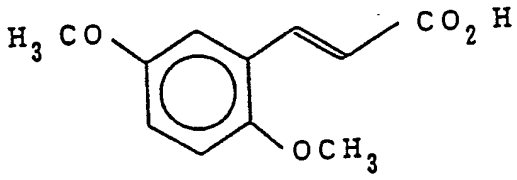


The ester (2.56 g), which was prepared with using the ester prepared in reference example 17 by the same procedure as reference example 10, was dissolved in ethanol. p-Toluenesulfonic acid (15 mg) was added to the solution. The solution was stirred for 40 min at room temperature. Few drops of triethylamine was added to the reaction solution. The reaction mixture was evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1) to give the title compound (1.93 g)

having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.10;
MS : m/z 419 (M^+), 363, 277, 259, 231.

Reference example 24

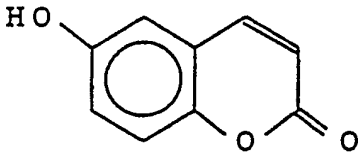
3-(1,4-dimethoxybenzen-2-yl)prop-2E-enoic acid



2,5-Dimethoxybenzaldehyde (1.7 g) was dissolved in pyridine (10 ml). Piperidine (0.2 ml) and malonic acid (2.0 g) were added to the solution. The solution was stirred for 1 hour at 85 °C and then for 3 hr. at 110 °C. The solution was cooled. Water (80 ml) was added to the solution. Conc. hydrochloric acid was added to the solution until pH of the solution was down to about 2. The crystals were deposited. The crystals were separated from the solution by filtration, washed with water and dried to give the title compound (1.97 g) having the fo.owing physical data.
NMR: δ 8.08 (1H, d, J = 16Hz), 7.08 (1H, d, J = 2Hz), 6.98-6.83 (2H,m), 6.53 (1H, d, J = 16Hz), 3.85 (3H, s), 3.80 (3H, s).

Reference example 25

6-Hydroxycoumarin



The carboxylic acid (1.97 g; prepared in reference example 24) and pyridine hydrochloride (12 g) were heated to 180-190 °C. The mixture was reacted for 3.5 hr. The reaction mixture was cooled and then dissolved in water. The solution was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 3 : 1 → 1 : 1). The obtained crystals were washed with a mixture of n-hexane and ethyl acetate (3 : 1 → 1 : 1) to give the title compound (751 mg) having the following physical data.
NMR: δ 7.67 (1H, d, J = 10Hz), 7.20 (1H, d, J = 8Hz), 7.05 (1H, dd, J = 8Hz, J = 1Hz), 6.90 (1H, d, J = 1Hz), 6.40 (1H, d, J = 10 Hz).

Reference example 26

6-(4-ethoxycarbonylbutyl)oxycoumarin